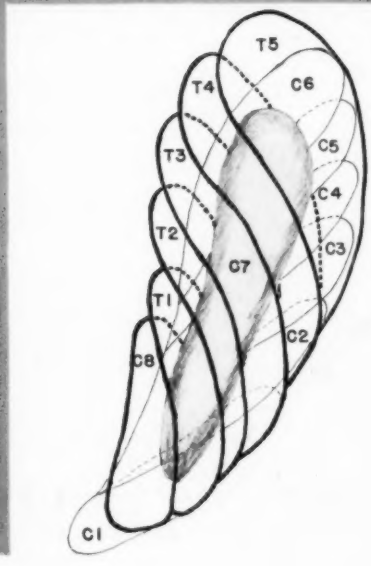
A.M.A.

Archives OF NEUROLOGY AND PSYCHIATRY

JANUARY 1956
VOLUME 75 NUMBER 1

From Liu, p. 67



AMERICAN MEDICAL ASSOCIATION Publication

COLONIAL HALL
One of Fourteen units in "Cottage Plan"

For Nervous Disorders

Maintaining the highest standards since 1884, the Milwaukee Sanitarium Foundation continues to stand for all that is best in the contemporary care and treatment of nervous disorders.

Photographs and particulars sent on request.

Josef A. Kindwall, M.D.
Carroll W. Osgood, M.D.
William T. Kradwell, M.D.
Benjamin A. Ruskin, M.D.
Lewis Danziger, M.D.
Russell C. Morrison, M.D.
James A. Alston, M.D.
Ellis Bonnell, M.D.

★

Waldo W. Buss, Executive Director

Chicago Office—1509 Marshall Field Annex Bldg.
25 East Washington St.—Wednesday, 1-3 P.M.
Phone—Central 6-1162

MILWAUKEE SANITARIUM FOUNDATION, INC.

Wauwatosa • Wisconsin

TABLE OF CONTENTS

VOLUME 75 JANUARY 1956 NUMBER 1

ORIGINAL ARTICLES

REGULAR DEPARTMENTS

A. M. A.
Archives of Neurology and Psychiatry

VOLUME 75 JANUARY 1956 NUMBER 1

COPYRIGHT, 1956, BY THE AMERICAN MEDICAL ASSOCIATION

EDITORIAL BOARD

HAROLD G. WOLFF, Chief Editor, Neurology
525 East 68th Street, New York 21

ROY R. GRINKER Sr., Chief Editor, Psychiatry
Institute for Psychosomatic and Psychiatric Research
29th Street and Ellis Avenue, Chicago 16

STANLEY COBB, Boston
CHARLES D. ARING, Cincinnati
JOHN WHITEHORN, Baltimore
BERNARD J. ALPERS, Philadelphia
PERCIVAL BAILEY, Chicago
WILDER PENFIELD, Contributing Member, Montreal

AUSTIN SMITH, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals

AMERICAN MEDICAL ASSOCIATION
Scientific Publications

The Journal of the American Medical Association. Weekly. Annual Subscription Price, $15.00.

Quarterly Cumulative Index Medicus. Issued Twice a Year. Subscription Price, Calendar year, $25.00.

A. M. A. Specialty Journals
Monthly

A. M. A. Archives of Internal Medicine. Paul S. Rhoads, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.

A. M. A. Archives of Dermatology. Herbert Rattner, M.D., Chief Editor, 104 S. Michigan Ave., Chicago. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Ophthalmology. Francis Heed Adler, M.D., Chief Editor, 313 S. 17th St., Philadelphia 5. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Surgery. Waltman Walters, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.25.

A. M. A. Journal of Diseases of Children. Robert B. Lawson, M.D., Chief Editor, 1000 N. W. 17th St., Miami 36, Fla. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Pathology. Paul R. Cannon, M.D., Chief Editor, Department of Pathology, University of Chicago, The School of Medicine, 950 E. 59th St., Chicago 37. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.

A. M. A. Archives of Neurology and Psychiatry. Tracy J. Putnam, M.D., Chief Editor, 450 N. Bedford Drive, Beverly Hills, Calif. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.50.

A. M. A. Archives of Otolaryngology. George M. Coates, M.D., Chief Editor, 1721 Pine St., Philadelphia 3. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.50.

A. M. A. Archives of Industrial Health. Prof. Philip Drinker, Chief Editor, Dept. of Industrial Hygiene, Harvard University School of Public Health, 55 Shattuck St., Boston 15. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.

Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

Published Monthly by

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $14.00

PARKINSONISM

Artane*

HYDROCHLORIDE

Trihexyphenidyl HCl Lederle

effective over long periods

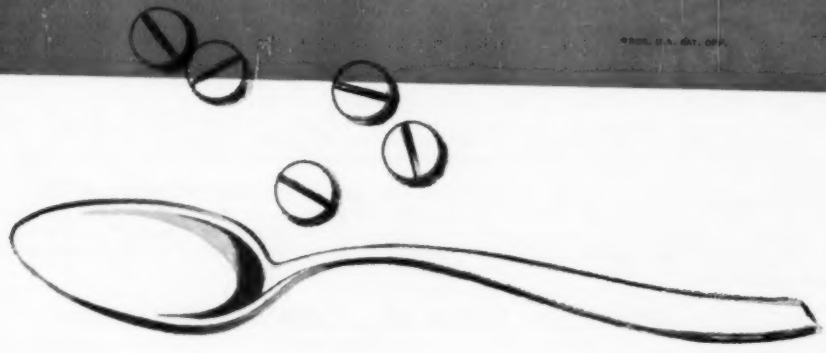
ARTANE is a strong antispasmodic, effective in all three types of Parkinsonism—Postencephalitic, Arteriosclerotic, and Idiopathic. Unlike certain other such drugs, it does not lose effectiveness when given over long periods. It is usually well tolerated, and has no deleterious effect on bone marrow function.

ARTANE is supplied in 2 mg. and 5 mg. tablets, and as an elixir containing 2 mg. per teaspoonful (4 cc.) Dosage: 1 mg. the first day, gradually increased, according to response, to 6 mg. to 10 mg. daily.

Lederle LEDERLE LABORATORIES DIVISION

American Cyanamid Company PEARL RIVER, NEW YORK

*REG. U.S. PAT. OFF.



Instructions to Contributors

Communications regarding editorial management, subscriptions, reprints, etc., should be addressed to Specialty Journals, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor of the Specialty Journal concerned. Articles are accepted for publication on condition that they are contributed solely to that journal.

An original typescript of an article should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. A carbon copy should be retained by the author. An article in English by a foreign author should be accompanied by a draft in the author's mother tongue. Improvised abbreviations should be avoided.

The main title of an article may not contain more than seventy characters and spaces; a subtitle may be of any length. The subtitle should be sufficiently detached from the main title that a punctuation mark as strong as a colon can be used in the Table of Contents to separate it from the main title; it must not begin with "with."

The author's name should be accompanied by the highest academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

A Case Report must be preceded by an introductory paragraph containing at least thirty words before the details of the case are given. To avert the possibility of legal action, patients' initials and hospital case numbers should not be published.

Material quoted from another publication must be quoted exactly if the original is in English—spelling, capitalization, punctuation, etc., unchanged. Material taken largely from another publication must be credited to the original author, whether quoted exactly or merely abstracted.

Each article should be accompanied by a summary in the present tense, presenting the main points of the article, but in somewhat more generalized terms than in the article itself.

If it is necessary to publish a recognizable photograph of a person, the photograph must be accompanied by written permission of the subject himself if an adult, or of the parents or guardian if a child, to publish his photograph. An illustration which has been published in another publication must be accompanied by written permission from the author and the original publisher to reproduce it in an A. M. A. Specialty Journal.

The maximum illustration allowance is ten illustrations within a total of 100 sq. inches or $100, whichever is of greater advantage to the author. When no restrictions are placed by the author upon cropping, reducing, and grouping, the publisher is often able to use twenty or more illustrations in one article with the $100 allowance. See an issue of this journal for examples. Oversized originals should be photographed and a print submitted. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author.

Any cut-off marks should be made on the margins (or mountings) rather than on the illustration itself. Charts and drawings should be in black ink on hard, white paper. Lettering must be large enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, an abbreviated title of the article, and top plainly indicated. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. ILLUSTRATIONS SHOULD BE UNMOUNTED.

References to the literature should be numbered in the order in which they are referred to in the text or listed in alphabetical order without numbers. A chronological arrangement, with all entries for a given year alphabetized according to the surname of the first author, may be used if preferred. References should be typed on a special page at end of manuscript. They should conform to the style of the Quarterly Cumulative Index Medicus, and must include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. Names of periodicals should be given in full or abbreviated exactly as in the Quarterly Cumulative Index Medicus. Reference to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication. Titles of foreign articles, if originally in a generally known Romance or Germanic tongue, must either all be in English translation or all be in the original language. Titles in other languages must be translated. The author must assume responsibility for the accuracy of foreign titles.

Matter appearing in the A. M. A. Specialty Journals is covered by copyright, but as a rule no objection will be made to its reproduction in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the A. M. A. Specialty Journals, or in any other publications issued by the Association, will not be permitted.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**

INDEX TO

NEUROPSYCHIATRIC INSTITUTIONS SPECIAL SCHOOLS and SANITARIA

Advertising in

A.M.A. Archives of NEUROLOGY and PSYCHIATRY

Display announcements of the following institutions appear regularly in A. M. A. Archives of NEUROLOGY and PSYCHIATRY. For advertisements of those institutions which run on an every-other month basis it would be necessary to consult the advertising section of a previous or *subsequent issue.*

Two articles in the April 30th issue of The Journal of the AMA [1,2] report on . . .

THE MILTOWN MOLECULE

an entirely new type of tranquilizer with muscle relaxant action— orally effective in

ANXIETY, TENSION and MENTAL STRESS

- not related to reserpine or other tranquilizers
- no autonomic side effects
- selectively affects the thalamus
- well tolerated, not habit forming, effective within 30 minutes for a period of 6 hours
- supplied in 400 mg. tablets. Usual dose: 1 or 2 tablets— 3 times a day

1. Selling, L. S.: J.A.M.A. **157:** 1594, 1955.

2. Borrus, J. C.: J.A.M.A. **157:** 1596, 1955.

Miltown®

U. S. Patent 2,724,720

the original meprobamate

2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate

A product of original research by

WALLACE LABORATORIES

New Brunswick *New Jersey*

LITERATURE AND SAMPLES AVAILABLE ON REQUEST

A.M.A. Archives OF NEUROLOGY & PSYCHIATRY

The Neurological Complications of Behcet's Syndrome

C. A. PALLIS, M.R.C.P. (London),
and
B. J. FUDGE, B.Sc. (Wales), M.B.
Cardiff, South Wales

Since 1930 a syndrome has gradually been recognized which is characterized by recurrent iritis (often with hypopyon) and ulceration of the mouth and genitalia. Most of the early reports are to be found in the French and German literature, but in the last few years the condition has attracted attention in this country and in America. Although usually first seen by the ophthalmologist, dermatologist or gynecologist, these patients may develop serious symptoms of considerable interest to the neurologist. We intend to review the main clinical features of this disorder and shall lay particular emphasis on the neurological disturbances that may occur, and even prove fatal. Two personally observed cases, with unusual cerebral and spinal complications, will be described. An attempt will then be made to define the pattern of involvement of the nervous system in this condition. The pathological evidence will be reviewed and comments made on the question of etiology.

HISTORY OF THE SYNDROME

Relapsing iritis with hypopyon has been known to ophthalmologists for nearly 200 years, and recurrent orogenital ulceration has been familiar to dermatologists for several decades. Many early descriptions refer to one or another of these aspects of the problem. Blüthe [11] (1908), however, and later Planner and Remenowsky [28] (1922) and Adamantiadès * (1930, 1931), mentioned the association of recurrent hypopyon-producing iritis with aphthae of the mouth and ulceration of the genitalia. Dascalopoulos [14] (1932) and Whitwell [34] (1934) recorded rather similar cases. Until then, most authors had considered the lesions of the mouth, eyes, and genitalia to be manifestations of such well-known diseases as syphilis, tuberculosis, or rheumatism. In 1937 Behcet,† Professor of Dermatology in Istanbul, ascribed these various symptoms to a specific morbid entity, whose characteristics he defined in a series of papers (1937, 1938, 1939, 1940), and which has since borne his name.

CLINICAL FEATURES

The mucocutaneous and ocular symptoms of this disorder are characteristically episodic. Bouts of activity may last from a week to a month, several attacks occurring in the course of a year. The condition is essentially chronic, and some cases have been "followed up" for as long as 20 years. The degree of constitutional disturbance accompanying each attack varies considerably, but

Received for publication July 27, 1955.
From the Bridgend General Hospital, and the Department of Neurology, Welsh National School of Medicine.

* References 1 and 2.
† References 6 to 9.

is usually slight, at least in the cases without involvement of the nervous system.

In the mouth, ulceration may develop on the lips, gums, tongue, palate, or the mucosa of the pharynx or cheeks. The number of lesions vary from one to a dozen or more. They are superficial, discrete, about the size of a lentil, and rather painful. They may show a grayish-yellow slough. An erythematous halo is sometimes seen about the lesions, but the surrounding mucosa is usually normal. Dysphagia may occur.

The genital lesions are usually confined to the labia or scrotum. They often occur in crops of about half a dozen and heal within three weeks. They are less common on the shaft or glans of the penis or on the vaginal wall or cervix, but are not infrequently found on the perineum. The lesions usually start as small vesicles or papules, which rapidly ulcerate. The ulcers may be no more than a few millimeters in diameter or may measure an inch or more across. They are of variable depth but are usually larger and deeper than the oral lesions. There is often a fetid gray slough. The remainder of the scrotum or vulva may show atrophy and scarring from previous bouts of ulceration. Slight inguinal adenopathy is usually present. Urethritis is not a feature. The lesions are tender, and pain on walking is often a prominent complaint.

The ocular symptoms usually develop unilaterally at first. The initial disturbance may consist of mild iritis only. Recurrence within a few weeks or months, either on the same or on the opposite side, is the rule, however. The visual acuity fluctuates, but the general tendency is for it to deteriorate steadily as the months go by. The ultimate prognosis with regard to useful vision is very poor. Many patients become blind within a few years of the first visual symptom, but, as will be pointed out, this is often the result of lesions farther back in the eye. The disorders of the anterior part of the uveal tract, upon which most attention was originally focused, are not the most crippling.

During the attacks, the oral, genital, or ocular symptoms may occur either alone or in various combinations. In many reported cases the mucocutaneous lesions have preceded the ocular ones by a considerable length of time, the longest recorded period being 10 years! Some patients may show early recurrent iritis, with ulceration for a while confined to either the mouth or the genitalia. In view of these facts, we have accepted, for the purpose of this review, the suggestion made by Curth [13] (1946) that a presumptive diagnosis of Behcet's syndrome is justifiable when two of the three main features are well in evidence. Such patients will usually develop the full syndrome in due course.

LESS COMMON SIGNS AND SYMPTOMS

Since Behcet's original case reports, certain other features have been recognized as occurring more or less frequently in this disorder. There are hints as to their occurrence even in the earlier literature. Erythema nodosum, for instance, may occur in a third of the cases (France and associates [15] 1950). More interesting, because of its possible bearing on the neurological complications to be described, is the not infrequent occurrence of thrombophlebitis, usually in the legs (Adamantiadès and Lorando,[4] 1949; Gray,[16] 1950). Attacks of arthralgia, sometimes with effusion, have also been recorded (Adamantiadès,‡ 1931, 1946; Behcet,[9] 1940; Curth,[13] 1946; Gray,[16] 1950; France and associates,[15] 1951; Silfverskiöld,[31] 1951; Phillips and Scott,[27] 1955). Acne and furunculosis are not uncommon. Cutaneous ulceration occasionally affects other parts of the body, in addition to the genitalia.

It has also been recognized that the ocular lesions need not be confined to the iris. Choroiditis, "retinitis," and optic neuritis may all occur and contribute to the serious prognosis with regard to vision. Isolated or recurrent thromboses of branches of the central retinal vein have been described (Jebejian and Kalfayan,[19] 1946; Thomas,[32] 1947; Adamantiadès and Lorando [4]). Retinal hemorrhages are not uncommon (Adamantiadès,‡ 1931, 1946; Behcet,[9] 1937; Schmidt,[29] 1940;

‡ References 2 and 3.

Knapp,[28] 1941; Gray,[16] 1950, Silfverskiöld,[31] 1951). Severe vitreous hemorrhages may seriously affect vision. Keratitis, conjunctivitis, and episcleritis have also been noted.

NEUROLOGICAL COMPLICATIONS

Neurological symptoms are uncommon. We have traced records of 11 patients who developed neurological symptoms, and these complications proved fatal in 4 instances. Involvement of the nervous system, therefore, carries a serious prognosis. These four deaths, all in young adults, are the only ones hitherto recorded in Behcet's syndrome.

In these 11 patients neurological complications usually occurred between the second and the fifth year of the disease and did not develop particularly early in the fatal cases. (The duration of the "neurological illness" in the latter group varied from three months to two years.)

A survey of all the cases suggests that, from a clinical point of view, the neurological disorder usually conforms to one of the following patterns:

1. A brain stem syndrome, which either may be episodic (Phillips and Scott[27]) or may progress, in an irregular manner, to death from bulbar paralysis (Gray[16]; Magni[25]).

2. A meningomyelitic syndrome (Silfverskiöld[31]) characterized by recurrent attacks of paraplegia or tetraplegia, heralded by fever, headache, and stiff neck and associated with marked polymorphonuclear pleocytosis in the C. S. F. Transient or terminal brain stem symptoms may occur in this group.

3. An organic confusional syndrome, either transient and associated with much agitation (Chauffard and associates,[12]) or progressing to a state of dementia with fits (Berlin[10]).

The case records of the 11 patients showing neurological complications will be summarized, as several of the original reports are in rather inaccessible journals and only a few are in English. It was found difficult to convey, in tabular form, a clear idea of the clinical features of this unusual disease, with its dramatic and diverse neurological manifestations. In all the patients described, syphilis had been excluded by examination of the blood and C. S. F., and these negative findings will, therefore, not be referred to in the protocols.

1. Brain-Stem Syndromes

Gray[16] (1950): A 26-year-old baker's assistant died after an illness lasting two years. While in the R. A. F. in Egypt, he had several attacks of an eruption resembling erythema nodosum, and later developed ulceration in the mouth, which recurred at about monthly intervals. These symptoms persisted after repatriation. He later suffered from relapsing iritis. Genital ulceration appeared shortly before he died.

A few weeks after the first visual symptom he noticed precipitancy of micturition and night sweats. He then developed weakness of the left leg and was admitted to hospital. Examination revealed thrombosis of a branch of the right retinal vein, vitreous opacities, and pyramidal signs in the left leg with normal sensation. The C. S. F. contained 25 cells/cu. mm. and 75 mg/100 cc. of protein. He then developed, one after the other, right third and fourth nerve palsies, palsy of the left superior rectus, nystagmus in all directions, and thermanalgesia about the legs. He eventually improved and was discharged from hospital after two months, but continued to have attacks of fever, erythema nodosum, oral ulceration, and iritis. He had to be readmitted after a few weeks. After a short while he became very ill, with high fever, occipital headache, and vomiting. Kernig's sign was positive. In rapid succession, there then developed left facial palsy; paralysis of conjugate gaze to the left, followed by complete ocular fixation; dysphagia, followed by complete bulbar palsy, and death from paralysis of the respiratory center. The C. S. F. during this last period contained 763 cells/cu. mm. and 70 mg/100 cc. of protein. There was no necropsy, but the terminal events were ascribed to a "spreading brain-stem thrombosis."

Magni[25] (1951): A young Italian, doing his military service in Libya, suffered re-

peated attacks of pain in the muscles and joints with fever. Within a few months bouts of blurring of vision appeared, first in the right eye and then in both. Examination revealed anterior uveitis, and in one fundus an area of periphlebitis, with exudate and hemorrhages. Recurrent ulceration of the tongue and lower lip then developed.

Five years later he noticed transient attacks of paresthesiae, paresis, and tremor of the left arm. A few months later there was a bout of high fever, with headache and dysarthria. Examination showed impaired elevation of the right eye, right facial weakness, tremor of the tongue, intention tremor in the left arm, ataxic gait, and bilateral pyramidal signs with extensor plantar responses. The C. S. F. contained 40 cells/cu. mm. and 60 mg/100 cc. of protein, but later the cell count fell to 9/cu. mm.

The neurological condition did not progress during the next two years, but the ocular symptoms continued to recur. During one such recurrence his gait deteriorated suddenly and markedly. A few days later he developed fever and had to be readmitted to hospital. In addition to the aforementioned signs, he now exhibited mental confusion, an expressionless face, bradykinesia, occasional tremor of the jaw and upper limbs, slight bilateral ptosis, and nystagmus to the right. The C. S. F. contained 18 cells/cu. mm.; the protein content had risen to 100 mg/100 cc., and the Pandy test was strongly positive.

Irregular pyrexia continued for the next three months. He finally lapsed into stupor, developed a high, continuous fever and diffuse tremulous movements, and died of cardiovascular collapse. The necropsy findings will be referred to further on.

Phillips and Scott [27] (1955): A woman of 27 had had ulcers in the mouth for over a year and vulval ulcers for 10 months and recurrent swelling of ankles and wrists. She developed a left facial palsy and complained of blurred vision, headache, vomiting, and dizziness. Examination revealed a blurred right optic disc with dilated retinal vessels, sustained horizontal and vertical nystagmus, facial palsy of lower motor neurone type absence of abdominal reflexes, ataxic gait, and equivocal plantar responses. The authors state that "the attack was transient, but minor recurrences have taken place."

Meningomyelitic Syndromes

Silfverskiöld [31] (1951) reported three patients with Behcet's syndrome, complicated by striking recurrent neurological disorders. One case proved fatal.

Case 1.—A male mechanic, aged 22, developed recurrent ulceration of the scrotum and tongue. Vision then began to fail in the left eye, and exudates in the vitreous were noted. The right eye was affected within a few months. Two years later there was bilateral hypopyon, and after six years no useful vision was left. He suffered repeated attacks of erythema nodosum during this period.

Seven years after the onset of his illness he developed fever, headache, disorientation, slurring of speech, numbness of the right arm and leg, and attacks of pathological laughter and crying. Examination revealed right hemiparesis and some ataxia of the right arm. The C. S. F. contained about 60 cells/cu. mm. (18% polymorphonuclear cells). Pandy reaction positive. He improved for a month, but then developed weakness of the left leg and difficulty with speech and swallowing. Improvement again set in and lasted several weeks. Further relapse then occurred, heralded by severe headache. He was admitted to hospital with right hemiplegia, the arm being markedly affected. There was dysphagia and dysarthria with bilateral pyramidal signs. Sensation was unaffected. He gradually recovered, sufficiently to get about without support, although virtually blind. Two years later severe paraplegia developed, with paralysis of the bladder and recurrence of pleocytosis in the C. S. F.

Case 2.—During a febrile illness, another mechanic, aged 19, had suffered from papillitis and bilateral choroidoretinitis with grossly impaired vision. The C. S. F. was found to contain 19 cells/cu. mm. The visual disorder recurred, and vitreous exudates appeared.

A year later he developed headache and spastic weakness of the right leg. The C. S. F. showed a pleocytosis of 1260/cu. mm. (80% polymorphonuclears). Within a fortnight the paresis had improved remarkably and the cell count had fallen to 5/cu. mm. He relapsed two months later and could no longer stand. There were signs of spastic paraplegia, but sensation in the lower limbs was unaffected. He again improved to the point of getting about with support. A fluctuating pleocytosis of the C. S. F. was recorded. After a few months oral ulceration occurred. He then fairly rapidly developed a right sixth nerve palsy, bilateral facial weakness, and quadriplegia. He died in hyperpyrexia. The terminal episode lasted only five days. The necropsy findings will be referred to further on.

CASE 3.—A 28-year-old woman had suffered from recurrent oral ulceration for many years. She later developed bilateral relapsing iritis with hypopyon.

Two years after the onset of visual symptoms she fell ill with high fever, headache, stiff neck, arthralgia, and spastic paresis of the right leg, with difficulty in micturition. The C. S. F. contained 257 cells/cu. mm. (31% polymorphonuclears). After a month her bladder symptoms had subsided and the C. S. F. was normal. A year later she again became febrile. The gait was staggering; she dragged the right foot and was clumsy with both hands. There was moderate paresis of the right leg with impaired sensation and reflex signs of spastic paraplegia. The left arm exhibited intention tremor. She improved. A little later another meningomyelitic episode occurred (with recurrence of bladder symptoms, increase of weakness of the right leg, and cerebrospinal pleocytosis), from which she recovered. The fourth and fifth attacks occurred four and seven months later, respectively, with weakness of both legs and of the left arm, and pleocytosis of the C. S. F. (322 cells/cu. mm.). Vaginal ulceration then developed. After an additional 18 months, during which she remained ambulant but continued to have severe recurrent iritis, she had a sixth myelitic attack, again with meningeal symptoms, but this time with disorientation, severe spastic quadriplegia, and a pleocytosis of 7500 cells/cu. mm. The outcome of this attack is not mentioned.

CONFUSIONAL SYNDROMES (? ENCEPHALITIC)

Chauffard, Brodin, and Wolf [12] (1923): A 28-year-old Frenchwoman developed recurrent ulceration of the mouth and labia majora. After six weeks erythema nodosum broke out on the arms. Several joints began to ache. There was fever and headache. Three weeks later mental changes gradually developed—first mutism and later considerable agitation and confusion. There were no focal neurological signs, and the C. S. F., although under increased pressure, had a normal content of protein and cells. She must have presented quite a nursing problem, as the authors record *"la malade injure le personnel, le mord, lui jette à la tête tout ce qu'elle trouve sous sa main."* The whole episode cleared up in two months. No follow-up is reported. The authors comment that the eruption had none of the features of herpes simplex. They considered the disorder infectious in origin and related to the *ectodermoses neurotropes.*

It is perhaps debatable whether this case was, in fact, one of Behcet's syndrome.

Berlin [10] (1944): A 28-year-old Jewish laborer, in Palestine, died after an illness lasting five years. For the first three years the only complaint was of recurrent ulceration of the mouth and genitalia. He then developed bilateral relapsing iridocyclitis with hypopyon.

Eighteen months later he became apathetic, confused, and disoriented. He complained of headache and dizziness. These symptoms increased over a period of three months. He then developed fits, lapsed into coma, and was admitted to hospital. His limbs were flaccid; the reflexes sluggish or absent, and he did not respond to painful stimuli. The C. S. F. contained 95 cells/cu. mm. (40% polymorphonuclears) and 49 mg/100 cc. of protein; Pandy test positive. He died four days later. The necropsy findings are referred to further on.

Miscellaneous Cases.— The following three cases are more difficult to classify, but are included for the sake of completeness.

Knapp [23] (1949): A Swiss woman aged 29 developed recurrent blurring of vision, affecting first one eye, then both. There were retinal and vitreous hemorrhages. Two years later she noticed headache, impairment of memory, clumsiness of the upper limbs, and dysarthria. Examination revealed ataxia of the arms, unsteady gait, exaggerated knee jerks, but retained abdominal responses. Sensation normal. Romberg sign positive. She made a good recovery within a month and had not relapsed seven years later. Recurrent iritis with hypopyon and ulceration of the genitalia developed after a long interval.

Alm and Öberg [5] (1945): A 31-year-old man had suffered from recurrent oral ulceration since childhood. In the course of 1942 he suffered from 8 attacks of "acute central exudative retinitis" and from no fewer than 20 attacks of iritis. Scrotal ulceration then developed, and he later suffered from an eruption of erythema-multiforme type. Throughout the whole period of observation he was never free from ulceration in the mouth. In the same year he suffered from a meningeal illness, during which the C. S. F., sterile on culture, contained 5400 cells/cu. mm. (84% polymorphonuclears). He made a good recovery but a year later had to be readmitted for "acute encephalitis," the main feature of which was "severe vertical nystagmus." The C. S. F. on this occasion contained 17 cells/cu. mm. He again recovered. No follow-up is reported.

Thomas [32] (1947): The patient described by this author is usually mentioned, in reviews of Behcet's syndrome, as having developed neurological complications in the course of his illness. We consider this opinion open to doubt.

A man of 29 had suffered from recurrent oral ulceration for eight years. He developed repeated attacks of iritis with hypopyon, and later choroidal changes. Within a couple of years vision in each eye had been reduced to perception of light only. In the course of the illness he developed severe bitemporal headache, nausea, and "equivocal eye signs," but no other neurological abnormalities. The C. S. F. was normal in composition but under a pressure of 250 mm. An encephalogram was normal. The headache fluctuated over many months, during which time both eyes had to be enucleated because of painful glaucoma. Scrotal ulceration eventually developed.

REPORT OF CASES

Our own two cases will now be discussed. The first presented a myelitic syndrome, rather unlike those previously recorded, and the second a progressive striatal and pyramidal syndrome with brain stem signs.

CASE 1.—Man, aged 47. *Recurrent iritis (bilateral) for 4 years; keratitis; recurrent ulceration of genitalia, legs, and forearms for 10 months; spastic paraplegia of sudden onset; flexor spasms; retention of urine. Cystostomy. C. S. F. forming gel (protein 5200 mg/100 cc.). Myelographic features of arachnoiditis. Plasma fibrinogen, 700 mg/100 cc.*

A miner aged 47, was transferred to the Neurological Department of Cardiff Royal Infirmary on Feb. 17, 1954. Had attended the Ophthalmic Department in 1949 for right-sided iritis. Later developed iritis on the left side, followed by keratitis.

In April, 1953, ulceration started near the glans penis and on the scrotum. Ulcers had been recurring at intervals of a few weeks, healing slowly. There had been little pain. Later, ulcers appeared on the knees, shins, and extensor surfaces of the forearms. No oral ulceration had been noticed.

In June, 1953, he developed low backache and had some difficulty in initiating micturition. He was admitted to Bridgend Hospital on Sept. 30, 1953, for biopsy of a penile ulcer. He was ambulant, and there were no abnormal signs on formal neurological examination. The C. S. F. protein was found to be 510 mg/100 cc. and the fluid clotted rapidly. An accurate cell count could not be performed. Lange curve 1555333320. Wassermann test negative. Normal manometric response to jugular compression. Repeated Wassermann and Kahn tests of the blood were negative (in several laboratories). During a three-month stay in hospital he received penicillin, bismuth, and neoarsphenamine (N. A. B.). Several new penile sores occurred during this period. A diagnosis of Behcet's syndrome was first suggested by Dr. Dyson, of Bridgend Hospital.

The patient did not complain of any weakness of his legs at this time. Shortly after his return home, severe weakness of both lower limbs devel-

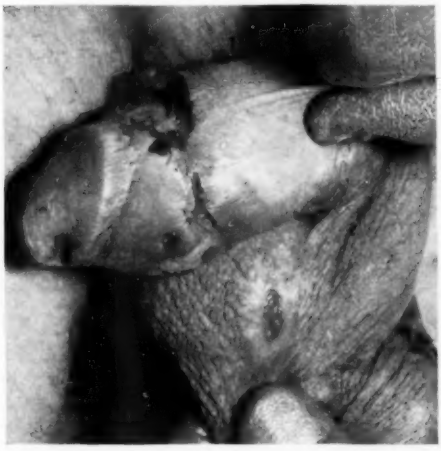
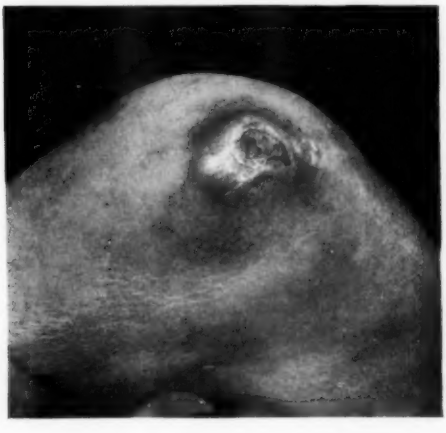


Fig. 1 (Case 1).—Ulceration of glans penis, prepuce, and scrotum. A biopsy specimen has been taken from one of the ulcers on the prepuce.

oped within a period of a few hours, the feet became "ice-cold" and numbness spread to waist level. There was marked difficulty in initiating micturition. Flexor spasms occurred, but he remained in bed, at home, for five weeks. He was readmitted to Bridgend Hospital, toward the end of January, 1954, on account of complete retention of urine. Suprapubic cystostomy was performed, and he was transferred a few days later to the Cardiff Royal Infirmary.

Examination showed an ill-looking, pale, thin, febrile man, with sacral bedsores. There were ulcers on the glans penis, under the prepuce, and on the scrotum (Fig. 1), on the right knee (Fig. 2),

Fig. 2 (Case 1).—Cutaneous ulceration over right knee. Lesions of this type are rare in Behcet's syndrome.



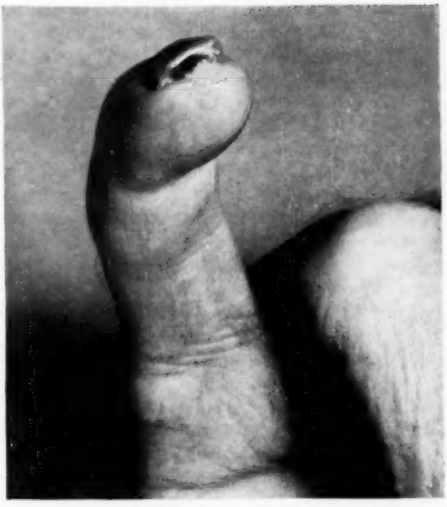
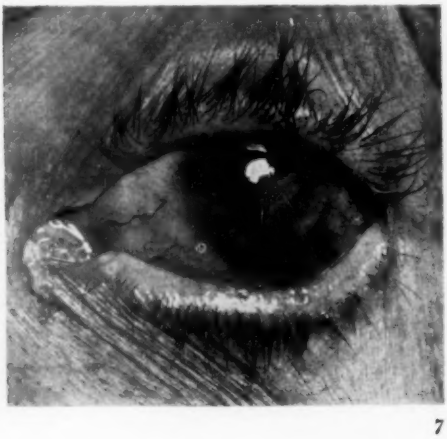


Fig. 3 (Case 1).—Small area of dry gangrene under nail of right little finger. Similar changes were present in several other fingers.

above the right external malleolus, on the anterior aspect of the right thigh, and on the extensor surface of the right forearm. There were small areas of dry gangrene under several fingernails (Fig. 3). An almost healed ulcer was observed on the palate. No furunculosis or erythema nodosum. The epitrochlear glands were palpable, and firm, enlarged nodes were felt in both axillae and in the groins. The liver was slightly enlarged.

There were no signs of organic mental deterioration. Visual acuity was 6/12 on the right, but on the left, on the side of keratitis (Fig. 4), it was

Fig. 4 (Case 1).—Keratitis of left eye. The residua of previous iritis can be seen in the irregularity of the medial border of the pupil.



reduced to counting fingers. The right fundus appeared normal. There was a brisk pupillary response to direct light in the right eye, and the pupil appeared normal in size. No abnormal neurological signs in the upper limbs. There was marked weakness of both legs, which could only just be elevated off the bed. Sustained patellar and ankle clonus and extensor plantar responses. Flexor spasms occurred frequently. There was weakness of the lower abdominal muscles. The abdominal reflexes were absent in the lower quadrants and retained in the upper. All modalities of sensation were depressed below the T10 dermatome, the loss being maximal, bilaterally, from T11 to L2. There was a suggestion of "sacral sparing." He was constipated but could void urine per urethram.

Investigations.—Hb. 11.6 gm.; red cells 4,500,000; leucocytes 9600/cu. mm.; differential count normal; E. S. R. 35 mm. in one hour (Wintrobe); blood urea 32 mg/100 cc.; Wassermann and Kahn tests negative. Total plasma protein 6.7 gm/100 cc. (albumin 3.2 gm/100 cc.; globulin 2.8 gm/100 cc.; fibrinogen 700 mg/100 cc.). This figure was confirmed by direct estimation. Urine: 20-30 pus cells per high-power field. Culture yielded Escherichia coli.

Radiographs did not show any periosteal reaction under the various sites of cutaneous ulceration. There was erosion, however, of the terminal phalanges, in those fingers in which small areas of dry gangrene had appeared under the nails.

C. S. F. could only be obtained from the lumbar theca by aspiration. The fluid was turbid and clotted quite solidly within four minutes, forming a gray gel. A specimen was collected in citrate and was shown to contain a total protein of 5200 mg/100 cc. (albumin 2300 mg/100 cc.; globulin 2500 mg/100 cc., and fibrinogen 400 mg/100 cc.). The specimen contained a few cells, but an accurate count was not possible. Cisternal C. S. F. contained 70 mg/100 cc. of protein and less than 5 cells/cu. mm. The Lange curve on this sample was 4444322110 and the Wassermann test negative.

In view of the marked difference in protein content of the two samples and of the definite sensory level, cisternal myelography was performed. The streaky pattern and behavior of the myodil on screening suggested adhesions narrowing the available subarachnoid space over a large area in the spinal canal, in the lower thoracic and lumbar regions.

The patient received 200 mg. of cortisone daily for 5 days, followed by 100 mg. daily for 10 days, without apparent improvement. A fresh ulcer on the leg developed during this period, from which a biopsy specimen was taken.

Comment.— An extremely high C. S. F. protein occurred in this case, in the absence of total myelographic obstruction. The suddenness with which the paraplegia developed is suggestive either of a vascular disturbance or of an acute myelitis of infectious or allergic type. A considerably raised C. S. F. protein is consistent with these various possibilities but points perhaps mainly to spinal venous occlusion.

Features shown by this patient, and hitherto unrecorded in Behcet's syndrome, are spinal arachnoiditis, a raised plasma fibrinogen, and digital gangrene with rarefaction of the underlying bone.

CASE 2.—*Man, aged 44. Recurrent ulceration of mouth and genitalia, 15 years; progressive stiffness of right arm and both legs, 18 months; intellectual deterioration; Parkinsonian features; pathological laughter and crying; dysarthria; spastic tetraparesis with predominant rigidity; nystagmus; gaze pareses; jaw clonus. C. S. F.: protein 90 mg/100 cc.; 6 cells/cu. mm. (50% polymorphonuclears). Plasma fibrinogen: 800 mg/100 cc.*

A 44-year-old miner was admitted to the Neurological Department, Cardiff Royal Infirmary, on March 4, 1955. He had suffered from painful crops of ulcers in the mouth and on the scrotum for some 15 years. At first, two or three lesions would occur at a time, but lately outbreaks often consisted of as many as a dozen ulcers, which would take two or three weeks to heal. He had had to give up work in 1953 because soreness in the perineum had prevented him from getting about.

Over a period of 18 months he had developed increasing stiffness and awkwardness in the right arm and walking had become slow and shuffling. He had not experienced any pain in the limbs. Some mental deterioration had been noticed, and for about a year he had been liable to outbursts of unwarranted laughter and weeping. Sphincter control had not been affected. No history of iritis. No family history of neurological disorder.

Examination showed a well-covered man of good color, with a fatuous, rather expressionless, greasy face. He had little insight, was euphoric and mildly catatonic, and his speech was slow and stiff. He cerebrated slowly. Pathological laughter and weeping could easily be elicited. A shallow ulcer was seen at the angle of the mouth, on the right side, and there was some scarring about the palate. A whole crop of recent ulcers were scattered on the posterior surface of the scrotum (Fig. 5), which also showed considerable scarring. The trunk and arms showed slight acne. There was no adenopathy, and no abdominal viscera were palpable.

The optic discs were rather pale and their edges unusually sharp. Corrected visual acuity was 6/12

R. E. and 6/9 L. E. Conjugate gaze was poorly maintained laterally, and conjugate upward gaze was defective. A sustained, "jelly-like" nystagmus occurred on attempting to look up and was also present on looking to the right. Coarse nystagmus was obvious on looking to the left. The jaw jerk was very brisk, with clonus at times. The face was spastic. No reflex pouting or sucking. Repetitive tongue movements were laboriously performed, although there was no obvious weakness. There was increased tone in the flexors of the neck and rigidity in all muscle groups of the right arm and of both legs (especially the right), with moderate adductor hypertonus of both thighs and bilateral spastic foot drop with contractures. No tremor. Power was slightly reduced in the affected limbs,

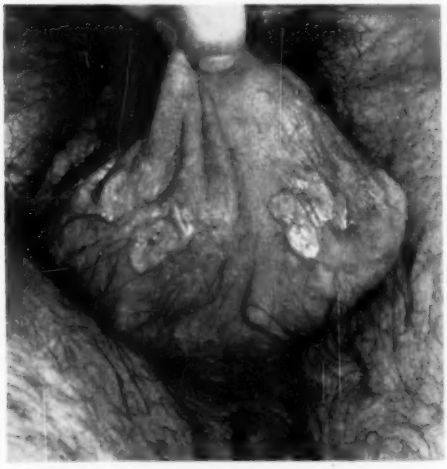


Fig. 5 (Case 2).—A recent crop of scrotal ulcers, typical of the lesions in Behcet's syndrome.

but most of the disability appeared due to rigidity rather than paresis. There was marked bradykinesia. His gait was awkward and stiff, but he could get about the ward unaided. No cerebellar signs could be demonstrated in the unaffected left arm. He was a poor sensory witness, but there were no obvious abnormalities. The reflexes were pathologically brisk in both arms, with slight extensor clonus at the right wrist. The abdominal reflexes were absent, the knee jerks brisk, the ankle jerks rather sluggish, and both plantar responses extensor.

Investigations.—Hb. 14.8 gm. per 100 cc. (100%); normal white cell and differential counts. E. S. R. 17 mm. in one hour (Wintrobe). Blood urea: 46 mg/100 cc.; Wassermann and Kahn tests negative. Clotting time (Dale and Laidlaw) 12 minutes (normal 5-12 minutes). Bleeding time (Duke) three minutes. Total plasma protein 7.5 gm/100 cc. (albumin 4.3 gm/100 cc.; globulin 2.7 gm/100 cc.; fibrinogen 500 mg/100 cc.). The electrophoretic pattern was normal. Several direct estimations of the plasma fibrinogen were performed, the readings varying from 200 to 800 mg/100 cc. The highest value was recorded within three days of the outbreak of a fresh crop of ulcers. Liver function tests normal. C. S. F.: protein, 90 mg/100 cc.; Pandy positive; Lange curve 1111100000; Wassermann reaction negative; cells 6/cu. mm. (50% polymorphonuclears).

Radiograms of the skull were normal. Films of the chest showed pneumoconiotic nodulation.

Progress.—Trihexyphenidyl (Artane) slightly lessened his rigidity, and he is now taking this drug regularly. Cortisone (100 mg. daily) was given for three weeks, but ulcers continued to occur. Courses of oxytetracycline (Terramycin), chlortetracycline (Aureomycin), and erythromycin have had no effect on the recurrent ulceration.

Comment.—This patient showed a type of neurological disturbance not previously recorded in Behcet's syndrome. There was an insidiously progressive disorder of mixed pyramidal and extrapyramidal type with mild organic dementia. In addition, he showed ocular signs suggestive of the more usual brain stem lesion. He resembled the first patient in showing, at times, an increase in the level of plasma fibrinogen.

PATHOLOGY

1. *Oral and Genital Lesions.*—Biopsy studies of the oral and genital lesions have often been performed but have yielded little information of value. The changes observed are usually nonspecific (as in our two patients). The oral ulcers may penetrate deeply into the mucosa propria, and leucocytic infiltration of the underlying musculature of the tongue has been described. The genital lesions are usually covered by purulent fibrinous exudate, and perivascular round-cell infiltration often extends deep into the corium, which may show "large and apparently thrombosed vessels" within areas of inflammatory infiltration (Berlin [10]). France and associates [15] reported on a biopsy specimen from a scrotal nodule prior to ulceration. The epidermis was intact. This

very early lesion was characterized by pronounced perivascular and interstitial edema and by diffuse interstitial infiltration with small mononuclear cells. The inflammatory cells tended to accumulate about the capillaries and venules, sparing the arterioles. Under fully developed scrotal ulcers, the vascular lesions were particularly prominent. The authors conclude that "histologically, these changes are non-specific and merely express an inflammatory process with prominent involvement of the smallest veins."

2. *Other Cutaneous Lesions.*—In a patient reported by Thomas [22] there developed, in addition to oral and genital ulceration, erythema-nodosum-like lesions on the thighs. Biopsy showed "an acute inflammation of a vein, with thrombosis." Many polymorphonuclear cells were seen in the thrombus, and the inflammatory process spread some distance into the surrounding tissue.

A biopsy specimen was also obtained from an erythema-nodosum-like lesion in a patient described by Karani.[21] It was reported as showing "a marked allergic reaction lying within the lower cutis and subcutis," with areas of polymorphonuclear cell infiltration, marked proliferation and thrombosis of vessels, and "fibrinoid degeneration of perivascular collagen" in places.

3. *The Eyes.*—Histological information about the ocular lesions is scanty. In Thomas' case both eyes had eventually to be enucleated. The retinae were detached; there was gross intraocular hemorrhage, chiefly subretinal, "but no certain evidence that the vascular thrombosis was the initial factor." In the patient reported by France and associates,[15] both eyes also had to be enucleated. There were degenerative changes in the choroid and retinae, which were partly detached and showed old hemorrhages. Heavy leucocytic infiltration was present in the ciliary body and iris. Fibrosis and scarring were prominent. Similar changes were also observed in Magni's patient, whose eyes, in addition, exhibited marked atrophy of the iris stroma and intense edema of the optic nerve with cellular infiltration and glial reaction. The choroidal atrophy, in this patient, was particularly marked in the region of a previously observed retinal periphlebitis. The eyes also had to be removed, after total blindness had set in, in the patients described by Adamantiadès [2] and Curth.[13] The histological changes were nonspecific.

4. *The Nervous System.*—Only three necropsies of patients with Behcet's syndrome are on record. The data are, unfortunately, rather incomplete. The investigators have rarely made use of the full range of modern histological techniques, and virus studies on material obtained post mortem have not been attempted. The necropsies are summarized below.

Berlin[10] (1944): Edema of the liver. (In one section slight focal round-cell infiltration was found.) Similar changes in the kidneys. The brain showed thickening of the basal meninges and, after fixation, poorly defined, small foci of softening in the region of the substantia nigra. On microscopy, both meninges and brain showed focal perivascular infiltration, consisting usually of round cells, but occasionally of polymorphonuclears. The central artery of the retina and its branches showed perivascular cuffing. The choroid and membranes of the optic nerve were also infiltrated. The spinal cord was edematous. The peripheral nerves showed nothing abnormal.

Silfverskiöld[31] (1951; Case 2): These was diffuse enlargement of the pons, the pyramids in particular appearing enlarged. The pallidum had an unusual blue-gray color. The cervical cord was "somewhat voluminous" and had a gelatinous appearance. Microscopy revealed widespread cellular infiltration of focal type, localized mainly to the peduncles, brain stem, and thoracic cord. At these sites, some axis cylinders were partially missing and "granulo-fatty" cells were seen. Perivascular round-cell infiltration extended far beyond these focal areas. Signs of meningitis were "only slight."

Magni[25] (1951): Slight external hydrocephalus with considerable meningeal thickening, particularly in the chiasmal region. Little or no change was found in the basal arteries. On section of the cerebral peduncles, there was noticed an "irregularity in form and in proportion of the substantia nigra." The spinal cord was normal.

Histological examination showed slight meningeal infiltration. Degenerative changes were observed in the neurones of the substantia nigra and basal ganglia, which also showed mononuclear infiltra-

tion and slight glial proliferation. Clusters of polymorphonuclear cells were seen around some blood vessels. No demyelination was found in the cerebral white matter.

We believe it significant that in none of these necropsy reports is mention made of occlusive changes occurring in the smaller blood vessels.

ETIOLOGY

The etiology of this disorder is for the moment unknown. The prevailing ignorance on this subject has been well reviewed by Phillips and Scott [27] (1955), who discuss some of the theories propounded from time to time. In our opinion, three hypotheses deserve special consideration, and the evidence in favor of each will be briefly discussed, together with possible objections.

(*a*) *Vascular Disorder.*—The idea that Behcet's syndrome may have a vascular basis is derived from the frequent occurrence of thrombosis in various systemic veins. As previously mentioned, the retinal veins may be involved, and thromboses of cutaneous veins were recorded in 25% of the 33 cases reviewed by France and associates.[15] The case reported by Thomas [32] is of particular interest in that thrombosis of the inferior vena cava occurred.

Occlusion of small arterioles and venules in the immediate border or base of the ulcers cannot be adduced as evidence of vascular disorder, as some have claimed. Such changes are common at the edges of many kinds of ulcers and would appear essential if exsanguination is not to occur. The thromboses occurring at some distance from the ulcer, and the preulcerative venous occlusions reported by France and associates [15] do, however, suggest that vascular factors may be important.

Certain features of our two cases are perhaps of relevance in this discussion: (*a*) Our first patient developed a myelopathy, possibly on a vascular basis, and, moreover, showed evidence of vascular insufficiency in several finger tips, and (*b*) at some time both our patients showed raised levels of plasma fibrinogen, likely to contribute to any thrombotic tendency that might have been present.

In all the previously recorded cases with neurological complications, however, neither the clinical nor the pathological evidence supported the hypothesis of a primary vascular disorder. Involvement of the brain or spinal cord was associated in most cases with polymorphonuclear pleocytosis in the C. S. F., and not infrequently with fever and signs of meningeal irritation. Vascular lesions were not a feature of the three reported necropsies.

It may finally be pointed out that anticoagulant treatment in Behcet's syndrome was tried by Silfverskiöld [31] and by Karani,[21] without benefit.

(*b*) *Allergy.*—The evidence on this count is unconvincing. Erythema nodosum, usually considered an allergic type of tissue response, occurs rather frequently in patients with Behcet's syndrome. Iritis for which no definite cause can be found is also often attributed to "allergy." The hypothetical allergen remains, however, completely elusive. The most that can be said for this theory is that the symptoms of Behcet's syndrome are strikingly recurrent and that, in this respect, they resemble those of certain allergic disorders.

Eosinophilia is not a feature of Behcet's syndrome. The only such occurrence we have found on record was in Silfverskiöld's third patient. This woman, toward the end of her illness, developed an eosinophilia of 35% in the peripheral blood (the total leucocyte count is not mentioned).

Certain neurological syndromes, clinically rather similar to those we have described, may arise in the course of acute disseminated encephalomyelitis. The classical forms of this disease are met after measles or vaccination, but cases also occur as sequelae to nonspecific respiratory infections or may even be seen without antecedent illness of any description. Miller and Evans [26] mention occasional acute encephalomyelitic syndromes in serum sickness, angioneurotic edema, and following sterile injections, and summarize

current opinion when they state that acute disseminated encephalomyelitis probably represents "a nonspecific allergic reaction of the nervous system to various antigens, chiefly of bacterial or virus origin, though possibly of other kinds as well."

Behcet's syndrome with neurological complications differs, however, from this illness in several respects. The natural history of the two conditions is dissimilar, the neurological complications in Behcet's syndrome tending to relapse or to progress. Moreover, in some of the cases we have reviewed, marked cerebrospinal pleocytosis (often polymorphonuclear) occurred. This is not a feature of acute disseminated encephalomyelitis.

The pathological evidence, as far as it goes, also suggests that the neural lesions in Behcet's syndrome are not those of acute disseminated encephalomyelitis. Whatever the immediate cause of the latter disorder (measles, vaccination, nonspecific respiratory infection, or an indeterminate factor), the pathological changes in the nervous system are fairly characteristic (Turnbull and McIntosh,[23] 1926; Greenfield,[17] 1930; Grinker and Bassoe,[18] 1931) and bear a striking resemblance to the histological findings in the experimental "allergic" encephalomyelitis produced in guinea pigs by repeated injections of homologous or heterologous brain tissue with adjuvants (Lumsden,[24] 1949). Perivascular infiltration, sometimes intense and of polymorphonuclear type, is recorded in all three necropsy reports of patients with Behcet's syndrome, and even edema of the spinal cord is described in one instance; but there is no specific mention of the myelinoclasis so characteristic of disseminated encephalomyelitis. The conditions, therefore, appear to be both clinically and pathologically distinct.

(*c*) *Infection.*—The theory of bacterial infection seems most unlikely. Swabs taken from the oral or genital lesions may grow a variety of bacteria, but these usually differ little from the predominant flora of adjacent parts of the patient's mouth or underwear.

With regard to virus infection, the evidence is conflicting. Behcet at one time claimed to have found inclusion bodies in the smears of hypopyon fluid and of exudate from the ulcers in the mouth. He believed the disorder a virus infection, although he was unable to demonstrate the pathogenic agent. Jensen[20] (1941) looked specifically for inclusion bodies but could not find any. Alm and Öberg[5] (1945) injected C. S. F. from their patients into rabbits, by the cisternal route and claimed the animals developed focal encephalitis, optic neuritis, uveitis, keratitis bullosa, and conjunctivitis. Curth[13] (1946) and Katzenellenbogen[22] (1946) were unable to culture virus from their cases. Sezer[30] (1953) claims to have isolated the virus responsible for Behcet's disease. Fluid obtained from the vitreous of an enucleated eye and subretinal serous fluid obtained by puncture in two other patients produced a growth of virus on the chorioallantoic membranes of fertile eggs and in allantoic fluid. After several passages the material was injected intracerebrally into mice (causing encephalitis), into the vitreous of rabbits (causing chorioretinitis and hypopyon), and intraperitoneally or subcutaneously into guinea pigs (causing a fatal hemorrhagic pneumonia). Sezer also claims that this material gave strongly positive complement fixation and neutralization reactions with the sera of 12 patients with Behcet's syndrome, but not with normal sera. He maintains that the failure of his predecessors was due to "the limitation of their investigations to the fluid of the anterior chamber and the exudate of the aphthae" and that "the pathological agent of the disease apparently resides in the posterior segment of the eye and is probably absent from the mouth and genital organs as well as from the hypopyon." These findings have not been confirmed to date.

In several of the cases we have reported the clinical features pointed to an acute infection of the nervous system. Other reports suggest a more chronic infection, either liable to periodic exacerbation or capable of

giving rise to progressive symptoms. The frequency of brain stem disorder, the description of changes in the substantia nigra in all three necropsy reports, and the development of Parkinsonian features in Magni's [25] case and in our second patient are all in keeping with the effects of a neurotropic virus with an affinity for the gray matter of the midbrain and basal ganglia.

It is often emphasized that Behcet's disease does not respond to any of the known antibiotics. If one considers the similar lack of effect of antibiotics on such conditions as poliomyelitis, rabies, and encephalitis lethargica, it will be seen that this is no argument against a viral agent being responsible.

Comment.—In the absence of additional, and particularly of more complete, pathological data, one can only speculate as to which of these hypotheses is the most plausible. We feel, however, that further search for an infective agent is the most likely to prove rewarding. It is not precluded that the presence of such an agent may manifest itself in more than one manner, in different parts of the body, and that the various views here discussed are not in fact as incompatible with one another as may at first appear.

SUMMARY

Behcet's syndrome consists of relapsing iritis, often with hypopyon, and recurrent attacks of oral and genital ulceration. Other symptoms occasionally appear. The characteristic clinical features of the disorder are described.

The nervous system may be affected, and the prognosis then becomes extremely serious. We review the 11 previously reported cases of neurological complications supervening in the course of this illness and record 2 further instances. Four cases proved fatal.

In both our cases we found raised levels of serum fibrinogen, an abnormality not hitherto recorded in Behcet's syndrome.

The following patterns of involvement of the nervous system are identified: (*a*) a brain stem syndrome, (*b*) a meningomyelitic syndrome, and (*c*) an organic confusional syndrome (possibly encephalitic).

The available pathological evidence is reviewed.

The pathogenesis of the neurological complications is discussed in some detail, in an attempt to clarify the etiology of the disease. It is concluded that neither the hypothesis of thrombotic disorder nor that of "allergic encephalomyelitis" will adequately explain the clinical and pathological data. There is increasing evidence that a virus, occasionally exhibiting neurotropic tendencies, is the cause of this illness.

Both our patients first came under the care of Dr. F. L. Dyson, of Bridgend Hospital, who made the diagnosis in each instance. He has permitted us to report his cases. Dr. J. D. Spillane gave help and encouragement, and Mr. R. Marshall made the photographs.

REFERENCES

1. Adamantiadès, B.: Comptes rend. Soc. méd. Athènes, p. 586, 1930.

2. Adamantiadès, B.: Sur un cas d'iritis à hypopyon récidivant, Ann. ocul. **168**:271-278, 1931.

3. Adamantiadès, B.: La thrombophlébite comme quatrième symptôme de l'iritis récidivante à hypopyon, Ann. ocul. **179**:143-148, 1946.

4. Adamantiadès, B., and Lorando, N.: Sur le syndrome complexe de l'uvéite récidivante, ou soi-disant syndrome complexe de Behçet, Presse méd. **57**:501-503, 1949.

5. Alm, L., and Öberg, L.: Animal Experiment in Connection with Behcet's Syndrome: Preliminary Report, Nord. med. (Hygiea) **25**:603-604, 1945.

6. Behcet, H.: Über rezidivierende, aphthöse, durch ein Virus verursachte Geschwüre am Mund, am Auge und an den Genitalien, Dermat. Wchnschr. **105**:1152-1157, 1937.

7. Behcet, H.: Considérations sur les lésions aphteuses de la bouche et des parties génitales ainsi que sur les manifestations oculaires d'origine probablement parasitaire et observations concernant leur foyer d'infection, Bull. Soc. franç. dermat. et syph. **45**:420-433, 1938.

8. Behcet, H.: A propos d'une entité morbide due probablement à un virus spécial donnant lieu à une infection généralisée se manifestant par des poussées récidivantes en 3 régions principales et occasionnant en particulier des iritis répétés, Bull. Soc. franç. dermat. et syph. **46**:674-687, 1939.

9. Behcet, H.: Some Observations on Clinical Picture of So-Called Triple Symptom Complex, Dermatologica **81**:73-83, 1940.

10. Berlin, C.: Behcet's Syndrome with Involvement of Central Nervous System: Report of a Case with Necropsy, Arch. Dermat. & Syph. **49**: 227-233, 1944.

11. Blüthe, L.: Zur Kenntnis des recidivierenden Hypopyons, Inaugural Thesis, Heidelberg, D. Straus, 1908.

12. Chauffard, A.; Brodin, P., and Wolf, M.: Stomatite et vulvite aphteuses, suivies de troubles démentiels passagers, Bull. et mém. Soc. méd. hôp. Paris **47**:841-844, 1923.

13. Curth, H. O.: Recurrent Genito-Oral Aphthosis and Uveitis with Hypopyon (Behcet's Syndrome): Report of 2 Cases, Arch. Dermat. & Syph. **54**:179-196, 1946.

14. Dascalopoulos, N.: Sur 2 cas d'uvéite récidivante, Ann. ocul. **169**:387-393, 1932.

15. France, R.; Buchanan, R. N.; Wilson, M. W., and Sheldon, M. B.: Relapsing Iritis with Recurrent Ulcers of the Mouth and Genitalia (Behçet's Syndrome): Review, with Report of Additional Case, Medicine **30**:335-355, 1951.

16. Gray, G. S.: The Triple Complex Syndrome of Behcet, Canad. M. A. J. **62**:597-599, 1950.

17. Greenfield, J. G.: Acute Disseminated Encephalomyelitis as Sequel to "Influenza," J. Path. & Bact. **33**:453-462, 1930.

18. Grinker, R. R., and Bassoe, P.: Disseminated Encephalomyelitis: Its Relation to Other Infections of the Nervous System, Arch. Neurol. & Psychiat. **25**:723-747, 1931.

19. Jebejian, R., and Kalfayan, B.: Le syndrome oculo-bucco-génital, Ann. ocul. **179**:481-491, 1946.

20. Jensen, T.: Sur les ulcérations aphteuses de la muqueuse de la bouche et de la peau génitale combinées avec les symptômes oculaires (syndrome Behcet), Acta dermat.-venereol. **22**:64-79, 1941.

21. Karani, S. B.: Behcet's Disease, Proc. Roy. Soc. Med. **46**:45-46, 1953.

22. Katzenellenbogen, I.: Recurrent Aphthous Ulceration of Oral Mucous Membrane and Genitals Associated with Recurrent Hypopyon Iritis (Behcet's Syndrome), Brit. J. Dermat. **58**:161-172, 1946.

23. Knapp, P.: Beitrag zur Symptomatologie und Therapie der rezidivierenden Hypopyoniritis und der begleitenden aphthösen Schleimhauterkrankungen, Schweiz. med. Wchnschr. **71**:1288-1290, 1941.

24. Lumsden, C. E.: Experimental "Allergic" Encephalomyelitis: On the Nature of the Encephalitogenic Agent, Brain **72**:517-537, 1949.

25. Magni, S.: Morbo di Behcet con manifestazioni meningo-encefalitiche: Relievi clinici ed istopatologici, Riv. oto-neuro-oftal. **26**:445-451, 1951.

26. Miller, H. G., and Evans, M. J.: Prognosis in Acute Disseminated Encephalo-Myelitis, with a Note on Neuromyelitis Optica, Quart. J. Med. **22**:347-379, 1953.

27. Phillips, D. L., and Scott, J. S.: Recurrent Genital and Oral Ulceration with Associated Eye Lesions: Behçet Syndrome, Lancet **1**:366-370, 1955.

28. Planner, H., and Remenovsky, F.: Beiträge zur Kenntnis der ulcerationen am äusseren weiblichen Genitale, Arch. Dermat. u. Syph. **140**: 162-188, 1922.

29. Schmidt, R.: Zum Krankheitsbild der rezidivierenden Hypopyon-Uveitis, von Graefes Arch. Ophth. **142**:185-202, 1940.

30. Sezer, F. N.: The Isolation of a Virus as the Cause of Behçet's Disease, Am. J. Ophth. **36**: 301-315, 1953.

31. Silfverskiöld, B. P.: Recurrent Uveitis (Behcet's Syndrome) and Encephalomyelomeningitis, Acta psychiat. et neurol. **26**:443-453, 1951.

32. Thomas, E. W. P.: So-Called Triple-Symptom Complex of Behcet, Brit. M. J. **1**:14-16, 1947.

33. Turnbull, H. M., and McIntosh, J.: Encephalomyelitis Following Vaccination, Brit. J. Exper. Path. **7**:181-222, 1926.

34. Whitwell, G. P. B.: Recurrent Buccal and Vulval Ulcers with Associated Embolic Phenomena in Skin and Eye, Brit. J. Dermat. **46**:414-419, 1934.

Small Localized Ultrasonic Lesions in the White and Gray Matter of the Cat Brain

J. W. BARNARD, Ph.D.
W. J. FRY, M.S.
F. J. FRY, M.S.
and
J. F. BRENNAN, M.S., Urbana, Ill.

The work reported here is a continuation of the study in progress at this laboratory of the effects of accurately controlled doses of ultrasound on the tissue of the central nervous system. Previous publications * were concerned with the production and study of ultrasonically produced lesions in white matter. It was reported that selective lesions of almost any desired shape can be produced at any depth in the brain without affecting any intervening tissue by positioning the focus of a beam of high-frequency sound in the region to be affected. The previous work was restricted to the study of relatively large white-matter lesions produced by irradiating the tissue in a number of positions in an appropriately chosen overlapping pattern of spots. This paper is concerned with the histological study of small lesions produced by irradiating the tissue in a single spot with focused beams. The dosage conditions necessary for producing selective small-size white- and gray-matter lesions are reported.

Accepted for publication Aug. 16, 1955.

Bioacoustics Laboratory, University of Illinois College of Engineering.

Supported by Contract Nonr-336(00), NR 119-075 with the Physiology Branch of the Office of Naval Research.

* References 1 to 3.

METHODS

The detailed experimental procedure for the surgical preparation and irradiation of the animal are included in previous publications.† The ultrasonic transducers are also briefly described in these previous papers.

Thirty-six cats were irradiated and examined histologically during the course of the work reported in this paper. The animals are prepared for irradiation by anesthetizing with sodium pentobarbital and mounting them in a stereotactic head holder. A longitudinal incision is made in the skin and underlying tissues, and an appropriate portion of the calvaria is removed under sterile conditions, but the dura is left intact. Since the sound must be conducted from the irradiator to the brain by a liquid, a bottomless pan (with sloping sides) rimmed with a flange at the edges of the open bottom is positioned and supported over the head of the animal. The skin edges from the longitudinal incision are pulled up over the flange on the pan, and a liquid-tight connection between the skin and the pan is made. The sterile degassed isotonic salt solution, which acts as the conducting medium for the sound, is then transferred into the pan. Figure 1 illustrates the arrangement of head holder, pan, and irradiator with a skull of a monkey mounted in the head holder. For the irradiation of deep structures, the ultrasonic irradiator is oriented stereotactically with respect to the head holder before placing the animal in the machine.[1] Positioning of lesions to be placed in the cortex or immediately below may be conveniently accomplished visually after surgical preparation of the animal and just preceding the filling of the pan with isotonic saline.

Since the purpose of this study was to determine the ultrasonic dosage conditions required to produce very small white- and gray-matter lesions of different degrees of selectivity (with respect to the various tissue components), the brain was irradiated with the focus of the beam in single, isolated positions. The duration of the irradiation at a single position is denoted as a shot. Usually more than one irradiated position was produced in the brain

† References 1 and 2.

of each animal. This is in contrast to our previously reported work on white-matter lesions of a variety of shapes and sizes produced by irradiating the tissue in a relatively large number of overlapping positions.‡ The focal spot of the sound beam is small enough so that by carefully controlling the dose it is possible to produce lesions involving a few cubic millimeters of tissue. Just prior to

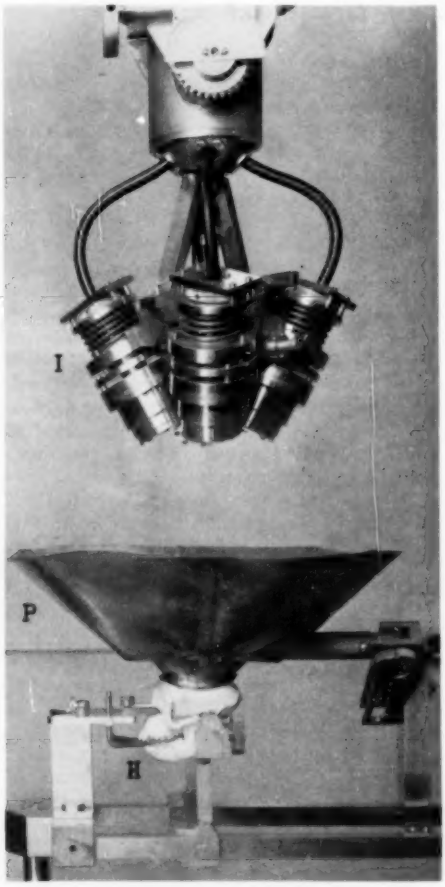


Fig. 1.—Arrangement of head holder (*H*), pan (*P*), and irradiator (*I*), illustrated with monkey skull mounted in the head holder.

irradiating an animal or a group of animals treated the same day, the instrument is calibrated by the method developed by Fry and Fry.[4]

The ultrasonic dosage is described by specifying the frequency (980 kc. for all animals), the duration of exposure, and the amplitudes of the acoustic particle velocity and pressure.

‡ References 1 and 2.

The ultrasonic gray-matter lesions were produced in the midline gray matter of the lateral gyrus. The center of the focal spot was positioned 2 mm. below the surface of the dura and 0.5 mm. from the midline. The white-matter lesions were usually produced in the subcortical white matter of the lateral gyrus 3 to 4 mm. from the midline. The focal spot was positioned 3 mm. below the dura at the chosen lateral position. The animals were killed under sodium pentobarbital at times after exposure varying from a minimum of about 5 minutes to a maximum of 12 days. They were exsanguinated and perfused with neutral 10% formalin in isotonic saline. The pertinent parts of the brain were embedded in paraffin and sectioned at 10μ. A series of every 40th section was prepared in Weil's myelin stain, and this series was examined in order to locate the lesions. Serial sections from the center of each lesion were then mounted, and alternate series were stained with Romanes' silver method, thionine, Heidenhain's hematoxylin, and Mallory's phosphotungstic-acid hematoxylin.

The procedure and instrumentation used in the studies pursued at this laboratory are distinctly different from the ultrasonic diathermy method and apparatus that have been employed by numerous other investigators § in irradiating the brain with ultrasound. The results reported in this and in preceding papers of this series ‖ cannot be obtained with diathermy procedures and apparatus. The pioneer work of Lynn and Putnam [8] introduced the use of the focusing crystal, but, unfortunately, the intervening skull prevented them from obtaining fruitful results.

RESULTS

Tables 1 and 2 list, for the white- and gray-matter lesions, respectively, the individual cats by number, amplitudes of acoustic pressure and particle velocity, the duration of exposure, the survival time of the lesion (time between irradiation and beginning of perfusion of the animal), and the type of lesion produced (classification terms defined below).

The results obtained from the histological study of both gray- and white-matter lesions are summarized in Tables 3 and 4, which are organized to exhibit the time sequence of events (following irradiation) and the degree of the selective response of the tissue elements to the dose of radiation.

The time of survival of the tissues after exposure to ultrasound is indicated along

§ References 5 to 7.

‖ References 1 to 3.

TABLE 1.—*Conditions of Irradiation, Survival Times, and Classification of Ultrasonic Lesions in White Matter*

Irradiation & Cat No.	Acoustic Pressure Amplitude,* Atm.	Acoustic Particle Velocity Amplitude,* Cm./Sec./10^2	Irradiation Time, Sec.	Survival Time	Lesion Classification
222-1	46	4.3	1.00	7 min.	None
222-2	46	4.3	1.50	6 min.	None
222-3	46	4.3	1.75	5 min.	None
209-1	48	4.4	1.00	9 min.	None
209-2	48	4.4	1.50	8 min.	None
209-3	50	4.6	1.75	7 min.	None
223-1	44	4.1	1.00	14 min.	None
223-2	48	4.4	1.50	13 min.	Heavy
223-3	48	4.4	1.75	12 min.	Heavy
207-1	48	4.4	1.00	.....	None
207-2	48	4.4	1.50	1 hr.	Light
207-3	48	4.4	1.75	.....	Heavy
215-1	48	4.4	1.00	.....	Medium
215-2	50	4.6	1.50	2 hr.	Heavy
215-3	49	4.5	1.75	.....	Heavy
205-1	50	4.6	1.00	.....	Light
205-2	46	4.3	1.50	6 hr.	Light
205-3	50	4.6	1.75	.....	Medium
212-1	46	4.3	1.00	.....	None
212-2	48	4.4	1.50	6 hr.	None
212-3	45	4.2	1.75	.....	Light
211-1	46	4.3	1.00	.....	Light
211-2	48	4.4	1.50	12 hr.	Medium
211-3	48	4.4	1.75	.....	Heavy
218-1	46	4.3	1.00	.....	Light
218-2	48	4.4	1.50	1 day	Medium
218-3	48	4.4	1.75	.....	Heavy
219-1	48	4.4	1.00	.....	Light
219-2	49	4.5	1.50	2 days	Medium
219-3	48	4.4	1.75	.....	Heavy
199-1	48	4.4	1.00	.....	None
199-2	48	4.4	1.50	4 days	Medium
199-3	48	4.4	2.00	.....	Heavy
221-1	45	4.2	1.00	.....	None
221-2	46	4.3	1.50	12 days	None
221-3	46	4.3	1.75	.....	Light

* The differences in the numerical values are significant on a comparative scale. However, the probable error in the absolute values of pressure and particle velocity does not exceed 10%.

the vertical axes of Tables 3 and 4. Horizontally, the Tables are subdivided into columns in which the changes in the individual tissue components are described. The light-, medium-, and heavy-lined columns designate the classification of the lesions (light, medium, and heavy for white-matter lesions and mild, moderate, and severe for gray-matter lesions). The single solid vertical lines above the vertical columns indicate that no histological change is observed in the tissue, and the dotted lines indicate an absence of information. Hatchure denotes that a particular tissue element, normally present, is absent. The statements appearing in the Tables are necessarily brief. The following semiquantitative designations apply to the description of the nerve cell bodies and glia: Very few, $\approx 1/10$ or less; few, $\approx 1/4$; some, $\approx 1/2$; many, $\approx 3/4$; most, $\approx 9/10$ or more. In the description of the nerve fibers and blood elements, the same terms are employed, but in a qualitative sense.

EFFECTS OF ULTRASOUND ON WHITE MATTER OF CEREBRUM

The lesions produced in white matter by ultrasound and described in this paper

TABLE 2.—*Conditions of Irradiation, Survival Times, and Classification of Ultrasonic Lesions in Gray Matter*

Irradiation & Cat No.	Acoustic Pressure Amplitude,* Atm.	Acoustic Particle Velocity Amplitude,* Cm./Sec./10^2	Irradiation Time, Sec.	Survival Time	Lesion Classification
225-1	48	4.4	2.00	8 min.	None
225-2	48	4.4	2.50	7 min.	None
225-3	48	4.4	3.00	6 min.	None
226-1	49	4.5	2.00	8 min.	None
226-2	46	4.3	2.50	7 min.	None
226-3	48	4.4	3.00	6 min.	None
210-1	48	4.4	2.00	13 min.	None
210-2	48	4.4	2.50	11 min.	None
210-3	48	4.4	3.00	10 min.	Moderate
208-1	48	4.4	2.00	16 min.	None
208-2	48	4.4	2.50	15 min.	Moderate
208-3	48	4.4	3.00	14 min.	Severe
206-1	49	4.5	2.00	.....	None
206-2	46	4.3	2.50	1 hr.	None
206-3	48	4.4	3.00	.....	Severe
214-1	48	4.4	2.00	.....	None
214-2	48	4.4	2.50	2 hr.	Moderate
214-3	48	4.4	3.00	.....	Severe
200-1	48	4.4	2.00	.....	None
200-2	48	4.4	2.50	6 hr.	None
200-3	48	4.4	3.00	.....	Severe
201-1	46	4.3	2.00	.....	Mild
201-2	48	4.4	2.25	6 hr.	Moderate
201-3	48	4.4	2.50	.....	Severe
197-1	50	4.7	2.00	.....	None
197-2	50	4.6	2.50	12 hr.	Severe
216-1	48	4.4	2.00	.....	Mild
216-2	48	4.4	2.50	1 day	Moderate
216-3	48	4.4	3.00	.....	Severe
220-1	46	4.3	2.00	.....	None
220-2	46	4.3	2.50	2 days	None
220-3	46	4.3	3.00	.....	Severe
202-1	49	4.5	2.00	.....	None
202-2	48	4.4	2.50	4 days	Mild
187-1	45	4.2	1.50	.....	None
187-2	45	4.2	2.50	12 days	Moderate
194-1	46	4.3	2.00	12 days	None
194-2	50	4.6	2.50	.....	Severe

* The differences in the numerical values are significant on a comparative scale. However, the probable error in the absolute values of pressure and particle velocity does not exceed 10%.

(Tables 1 and 3 and Figs. 2-10) are classified as light, medium, or heavy. A continuous gradation of severity of tissue damage may be obtained by varying the ultrasonic dose; however, lesions in the three categories defined below present an adequate picture of the type of selectivity and graded damage that has been observed. A lesion possessing a relatively homogeneous field of necrosis is called light (Fig. 2*A*). A lesion which contains a central region (island) staining like normal tissue surrounded by peripheral necrosis (moat) is called medium (Fig. 2*B*) if it does not encroach on neighboring gray matter. (It is convenient, from the viewpoint of ease of classification of white-matter lesions for dosage studies, to irradiate fiber tracts near the gray matter.) A lesion is classified as heavy (Fig. 2*C*) if it possesses an island and moat and also encroaches on neighboring gray matter. In general, the higher dosage effects are, of course, manifest by an increase in size of the lesion area.

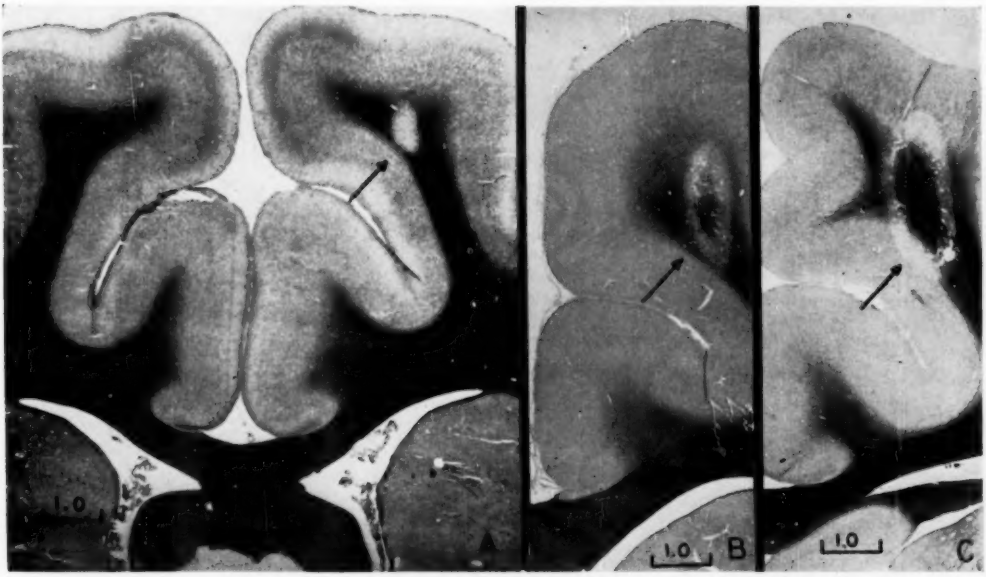
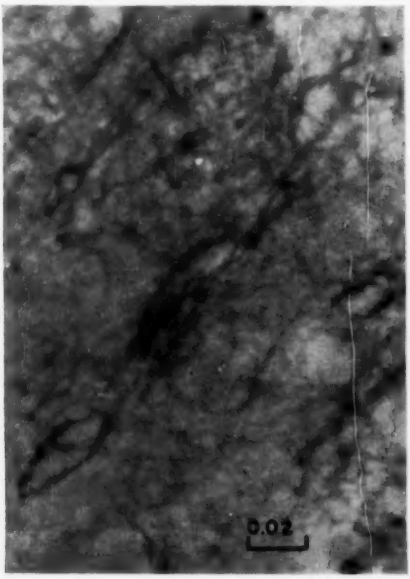


Fig. 2.—*A*, frontal section of a cat brain illustrating a light ultrasonic lesion in the subcortical white matter, Weil stain; *B*, a medium ultrasonic lesion in the subcortical white matter, Weil stain; *C*, a heavy ultrasonic lesion in the subcortical white matter (invading the cortical gray matter), Weil stain; scale units in millimeters.

Fig. 3.—A heavy lesion in the subcortical white matter of a cat brain 12 minutes after irradiation; Weil stain; scale unit in millimeters.

Fig. 4.—Swollen myelin sheaths in invaded gray matter in a heavy lesion 13 minutes after irradiation; Weil stain; scale unit in millimeters.



Early Changes.—No histological change is observed in the irradiated tissue of animals killed within five to nine minutes after exposure (six irradiated regions in two cats). Twelve to fourteen minutes after treatment the first evidence of lesion formation is visible. The moat in a heavy lesion (Fig. 3) is evident macroscopically as a lightly staining band which delineates, with its oval cross section, the area enclosing the island. All tissue components of the white matter in the island appear normal. Structures within the moat are characterized by their poor staining quality. In these perfused preparations no blood elements are seen in the blood vessels or in the tissue spaces, and the blood vessels appear normal.

Although heavy lesions in white matter are clearly evident macroscopically 15 minutes after irradiation, it is difficult to observe specific microscopic changes in the tissue structures by examination of the dense fiber tracts. However, in the neighboring gray matter, where discrete myelin sheaths can be discerned, it is possible to detect changes at this early stage. The sheaths exhibit swellings along their length, which give them a nodal appearance (Fig. 4). Some astrocytes and oligodendrocytes in both island and moat stain more palely than normal, and a few show slight swelling, and even fragmentation, in the moat.

One-Hour Lesions.—At one hour a heavy lesion shows a distinct moat of lightly staining material surrounding a central island. An example is illustrated in Figure 2*C*. In the moat there are many small and some large clear spaces. Some of the large spaces have ragged borders and loose debris in their interior. Such large spaces are not present in cat brains examined within 15 minutes after irradiation, thereby eliminating cavitation as a causative agent. One interpretation which seems possible is that fluid has entered the area from blood vessels and this fluid separates the possibly already weakened, necrotic tissue structure. Another interpretation is that liquefaction processes are in progress and the large clear spaces contain the products of this dissolution.

In silver-stained material there are only a few normal-appearing axis-cylinder fragments in the moat. Swollen and tortuous fragments persist, but the majority of the

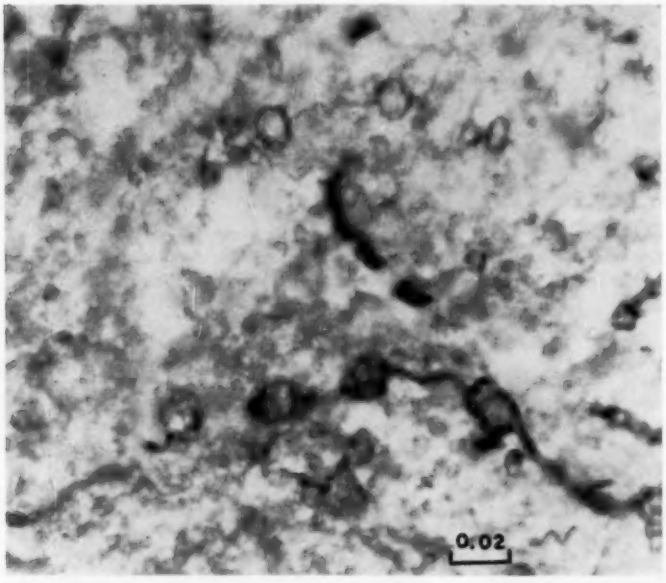


Fig. 5. — Bulbous myelin sheaths and isolated spheres in the invaded gray matter one hour after irradiation; Weil stain; scale unit in millimeters.

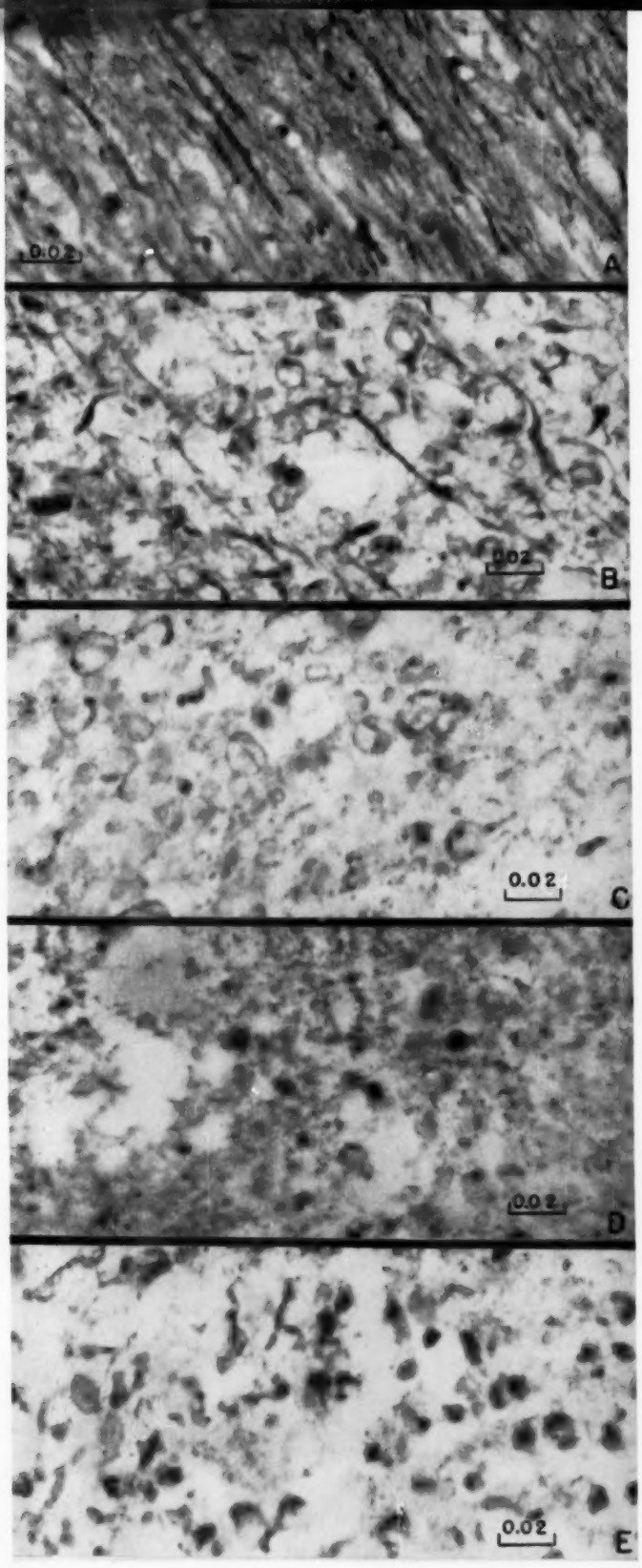


Fig. 6.—Stages of axis-cylinder degeneration in subcortical white matter of cat brain following ultrasonic irradiation; Romanes silver stain; scale units in millimeters. *A*, normal axis cylinders; *B*, early stage, showing axis-cylinder fragments, connected spheres, and debris; *C*, intermediate stage, showing isolated spheres and detritus; *D*, advanced stage, showing detritus and large clear spaces; *E*, terminal stage, showing glial scar and clear spaces.

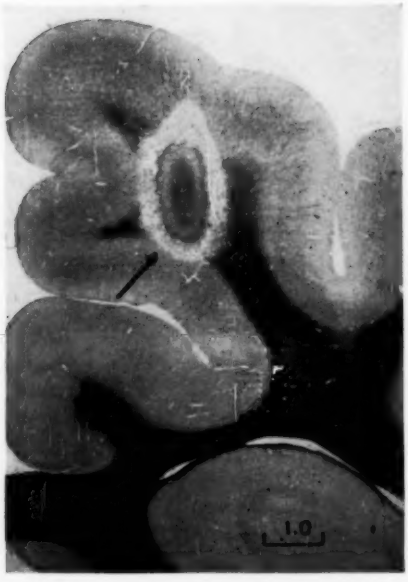


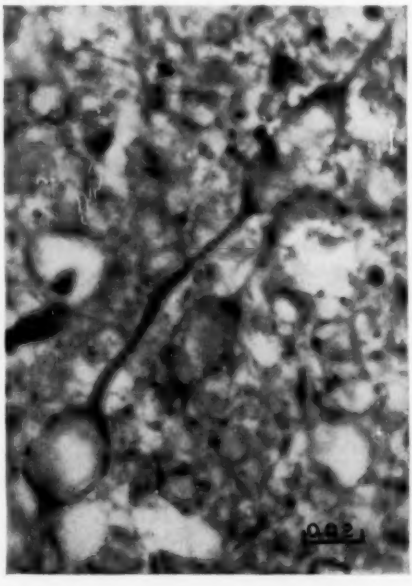
Fig. 7.—A heavy "laminated" lesion in the subcortical white matter of a cat brain killed four days after exposure; Weil stain; scale unit in millimeters.

axons are reduced to independent spheres, which are present in great numbers, as shown in Figure *6B*. The spheres, or circles as they appear in sectioned material, have a smooth, oval, or circular contour, and in some instances are empty. Others are filled with an argentophilic reticulum. Their outer wall is variable in thickness, depending apparently on the amount of myelin present. This sphere formation was described in detail by Ramón y Cajal.[9] The same appearance can be seen in Weil-stained material, as illustrated in Figure 5. (In order to illustrate clearly the structural detail of these spheres, a photomicrograph of the gray matter adjacent to the moat in the fiber tracts is presented.) Scattered among the hollow spheres, with walls whose thickness varies from that of a thin membrane to that of a normal myelin sheath, is a great deal of unidentifiable debris. This amorphous material probably results from axon destruction.

Intact blood vessels are present in the moat, and many are surrounded by large perivascular spaces. There are no blood elements present either inside the vessel walls or free in the tissue spaces. All the microglia cells and a few astrocytes are normal. Some of the oligodendrocytes and astrocytes are swollen, and a few of the former are fragmented, while some are missing or at least are not sufficiently intact to make identification possible.

The island inside the moat is virtually normal in appearance under low power for all stains. Even with high power, in silver-stained material, the axis cylinders appear normal. In material stained for myelin some of the sheaths have a nodal appearance, resulting from a segmental swelling along the length of the sheath. The blood vessels of the island are empty, as are vessels in all other areas of these perfused brains. The endothelium appears normal, and there are no blood cells free in the tissue spaces. The microglia appears normal and quiescent. Most of the astrocytes and oligodendrocytes are normal in appearance, but a few of them are pale and swollen.

Fig. 8.—Bulbous axis cylinder in the moat region of a medium lesion in the subcortical white matter 12 hours after irradiation; Romanes silver stain; scale unit in millimeters.



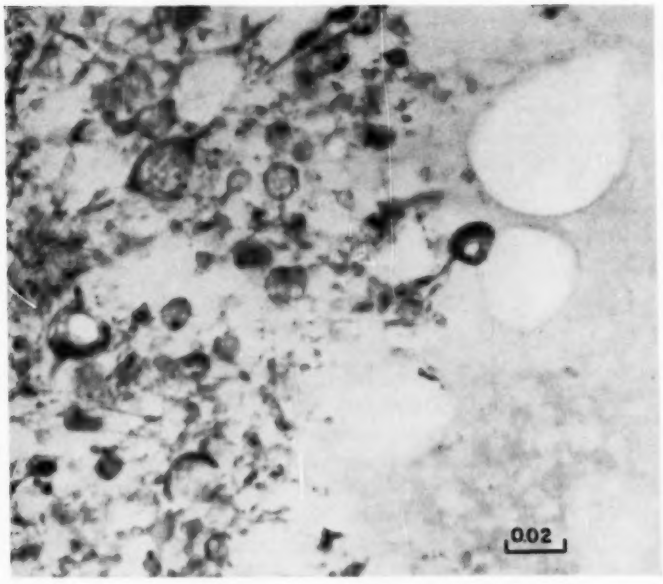


Fig. 9. — Retraction bulbs and digestive chambers at the periphery of a heavy lesion 12 hours after irradiation. The pale, structureless substance containing the clear spaces is the moat region of the lesion; Romanes silver method; scale unit in millimeters.

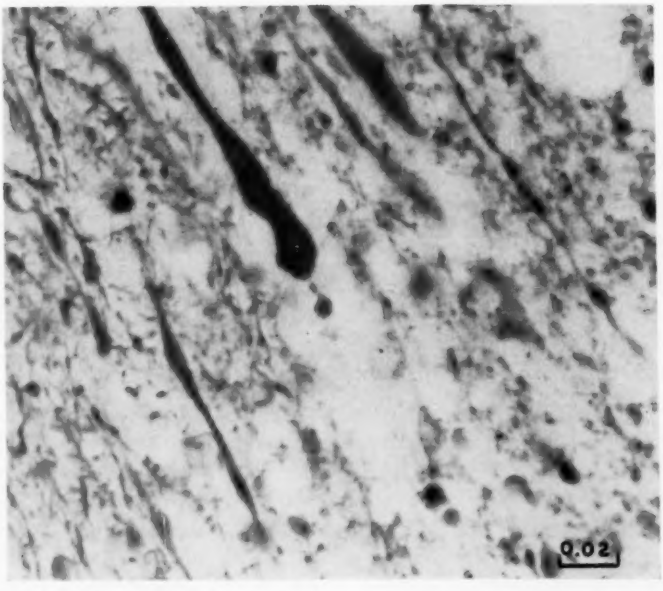


Fig. 10. — Retraction bulbs on nerve fibers of various calibers in the border zone of a heavy lesion one day after irradiation; Romanes silver method; scale unit in millimeters.

It is of interest to note that the island, which has received a greater dose of ultrasound than the moat, appears morphologically almost normal. The fibers in such an island may be similar to the preserved fibers described by Cajal[9] following traumatic lesions produced by knife cuts.

A light response, which is produced by a lower ultrasonic dose, is readily detectable at one hour. The entire area of the light

lesion resembles the moat of the heavier lesions; i. e., the tissue undergoes rapid morphological dissolution.

Later Changes.—The early changes described above establish the basic character of the lesions. The description of the later changes is organized into accounts of individual tissue components, in the following order: matrix, axis cylinders, myelin sheaths, glia, blood vessels and blood cells, and neighboring gray matter.

Matrix: The first change is observed 10 to 15 minutes after exposure (Fig. 3). The irradiated area stains weakly, and this method constitutes the current means of locating early lesions. The oval form of the focal region of the ultrasound beam is reproduced by the shape of this pale area. A heavy lesion at this time exhibits a rim of paleness which extends into the gray matter without distortion of the oval shape. Close examination reveals that the fiber elements are unchanged in the pale rim area, which will develop into the moat. The island matrix is normal in all respects. At one hour the moat area stains lighter than normal and fluid-filled holes appear. At two hours the moat has enlarged and clefts or large, irregular, fluid-filled spaces containing debris are found. Some of the fluid-filled spaces persist through the 12th day, which is the maximum survival period used in this study. Large lesions were produced in animals which were killed 30 days after exposure. These cases, reported upon elsewhere,[2] show either cyst-like cavities or closed glial scars.

Some heavy lesions exhibit the staining characteristics illustrated in Figure 7. The island is composed of concentric laminae, with an innermost core of almost normal-staining tissue surrounded by a zone of lighter-staining fibers, and this, in turn, is enclosed by a shell of fibers which stain like the inner core. This whole structure is surrounded by a moat area which is similar to that of lesions containing unlaminated islands. Close examination reveals no morphological difference in the elements of each of these lamina.

Axis Cylinders: In the Romanes silver preparations the axis cylinders appear normal for the first 15 minutes after irradiation. In the interval between 15 minutes and 1 hour many changes take place in high-dosage lesions such that in the moat area, one hour after irradiation, great destruction of axis cylinders is apparent. In light lesions no changes in the axons are seen at one hour, but two hours after irradiation changes are quite apparent. At lower ultrasonic doses than are required for the production of heavy lesions the tissue changes develop more slowly, but the alterations of the tissue components are of the same general character. It is not until two days, for the light lesions, and six hours, for the moat of medium lesions, that the destruction becomes comparable to that produced in the moat of a heavy lesion one hour after irradiation.

Although the sound intensity in the island is higher than in the moat, the rate of morphological destruction is slower. One hour after irradiation the axons are still normal in appearance, and it is not until four days in the medium reaction, and even later in the heavy response, that the island undergoes disruption comparable to that present in the moat region of heavy lesions one hour after exposure. The island resists autolysis in a manner comparable to the floating tissue blocks of Cajal. These blocks were produced in cat brains by means of two transversal cuts that isolated a length of axon from the remainder of the cell. These axons retained their morphological integrity for days following the lesion production. Complete hyalinosis took place only after two to three weeks.¶

In the axis cylinders the sequence of changes which occur is similar, but with different time rates, for all classifications of lesions (excluding preserved fibers in islands), as illustrated in Figure 6 (Figure 6*A* shows normal axis cylinders). The axon becomes swollen and tortuous initially (Fig. 4). The swellings resemble a chain of beads (Figs. 5 and 8), and the fiber breaks into

¶ Ramón y Cajal,[9] p. 635.

individual spheres (Fig. 6*B*). In the stage illustrated in Figure 6*C* almost all axis cylinders have taken the form of spheres. In Figure 6*D*, some spheres remain, much debris is present, and clear spaces appear in the matrix. After the debris has been ingested by phagocytes (gitter cells), a glial scar is formed, as illustrated in Figure 6*E*.

At the periphery of all lesions the severed axis cylinders form retraction bulbs and digestive chambers (Fig. 9), which are still present two weeks after exposure. The larger-caliber fibers retract farther into the border zone of the lesion than do the fibers of smaller diameter (Fig. 10).

Myelin Sheaths: Myelin sheaths show an initial response 12 minutes after irradiation. The sheaths, as seen in Weil stain, are slightly swollen (Fig. 4). One hour after exposure some of the myelin in the island has a nodal character, but the myelin in the moat at this time after a heavy ultrasonic dose is much more advanced along its path to destruction, appearing in the shape of hollow spheres. Many of these myelin spheres apparently enclose the spheres resulting from axis-cylinder degeneration that are seen in silver preparations. The myelin sheaths, similar to the axis cylinders, change more slowly in the island than in the moat, the principal difference being that the myelin exhibits a response to ultrasound earlier than do the axis cylinders.

Glia: The present study of the glia is only a general survey, since the particular techniques necessary to visualize the glial cells completely were not applied.[10] The following statements are based on a study of sections of the lesions stained with thionine, Heidenhain's iron-alum hematoxylin, Romanes' silver method, and Mallory's phosphotungstic-acid hematoxylin.

Changes in the microglia appear earlier in heavier lesions (when light lesions are compared with moats of the medium and heavy lesions), and at one day all lesions exhibit damaged cells and a reduced population. However, on the second day the microglial cells are more numerous than is normal and some are enlarged into phagocytes. They may be descendants of original resident cells or of invading cells. Four days after exposure the microglia cells (macrophages) dominate the field and are enlarged and laden with debris. Twelve days after irradiation a huge population of microglia cells is still present, but the debris is considerably reduced. From earlier studies # it is clear that at 30 days they are greatly reduced in number.

The astrocytes undergo great changes, which are first manifest in the moat of heavy lesions 10 minutes after irradiation by a slight swelling and paleness of the nuclei and a few broken membranes. Although swelling of the nucleus is characteristic of the physiological response which leads to cell division and further growth (del Rio Hortega and Penfield[11]), it is not necessarily indicative of such a response in this instance. One hour after exposure the changes are more pronounced. After four days the surviving cells have enlarged and are preparing to undergo division. At 12 days there are large astrocytes throughout the interior of the lesion, particularly in close proximity to the blood vessels. While they are not numerous, there are more toward the periphery, and a few are seen in the dividing stage.

The oligodendrocytes undergo degenerative changes, which appear 10 to 15 minutes after irradiation, i. e., pale-staining nuclei in the island and moat and a few fragmented nuclei in the moat. One hour later these changes have progressed, and at one day many have disappeared and the remainder are swollen and fragmented. At 4 days most of the oligodendrocytes have gone, and only some doubtful fragments remain, all having disappeared after 12 days.

Blood Vessels and Blood Cells: The blood vessels in the white matter do not appear to be altered morphologically by ultrasound. No erythrocytes appear in the matrix of any white-matter lesions even 12 hours after exposure, but by 24 hours some erythrocytes have escaped from the vessels in heavy

References 2 and 3.

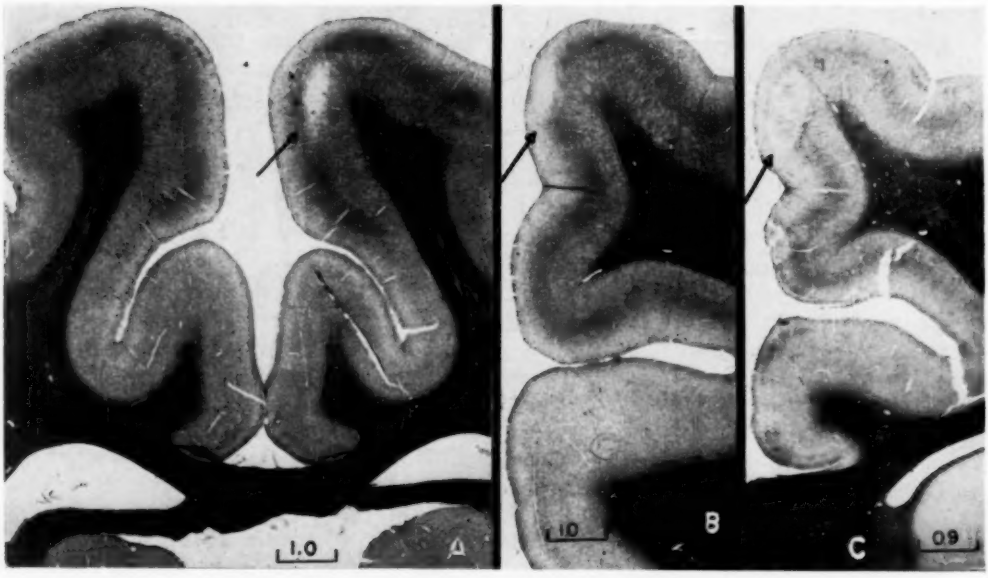


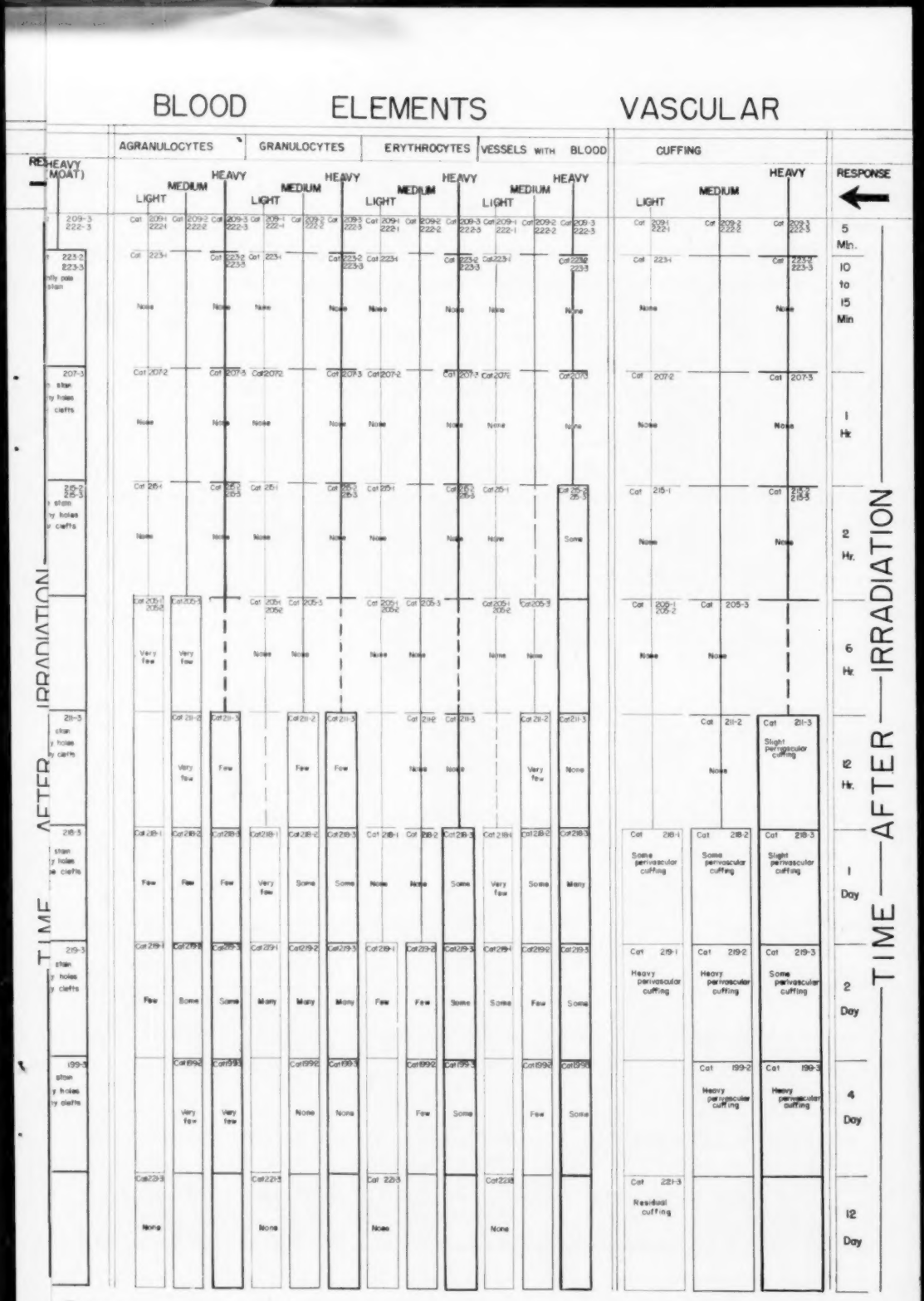
Fig. 11.—*A*, lesion produced by ultrasound in the intermediate layers of the cortical gray matter of a cat brain; phosphotungstic-acid hematoxylin. *B*, lesion produced by ultrasound in the surface layers of the cortical gray matter of a cat brain; phosphotungstic-acid hematoxylin. *C*, a severe lesion in the cortical gray matter of a cat brain 14 minutes after irradiation; phosphotungstic-acid hematoxylin. Scale units in millimeters.

lesions. Only in the heaviest lesions are some clusters present, which consist of as many as 100 cells in a section, but never more than one or two such clusters have been seen in any one lesion. Occasional erythrocytes are seen in the tissue of light and medium lesions during the time interval of one to four days after exposure.

Perivascular cuffing is first evidenced at 12 hours in the heavy lesions. The highest level seen, in the material available, is at four days. By 12 days it has regressed, and only residual signs are present. The hematogenous response, of which cuffing is a part, is observed by the presence of a few agranulocytes in the tissue, beginning at six hours. These reach their numerical peak at 2 days and then subside, so that none remain at 12 days. Granulocytes are first seen at 12 hours, increase to a maximum at 2 days, and have disappeared at 4 days.

Neighboring Gray Matter: During the production of a heavy white-matter lesion the neighboring gray matter is affected. In

Fig. 12.—Clefts in severe lesion six hours after irradiation. Romanes silver method; scale unit in millimeters.


BLOOD ELEMENTS
VASCULAR
AGRANULOCYTES
GRANULOCYTES
ERYTHROCYTES
VESSELS WITH BLOOD
CUFFING
LIGHT
MEDIUM
HEAVY
RESPONSE
5 Min.
10 to 15 Min
1 Hr.
2 Hr.
6 Hr.
16 Hr.
1 Day
2 Day
4 Day
12 Day
TIME AFTER IRRADIATION
Exposure

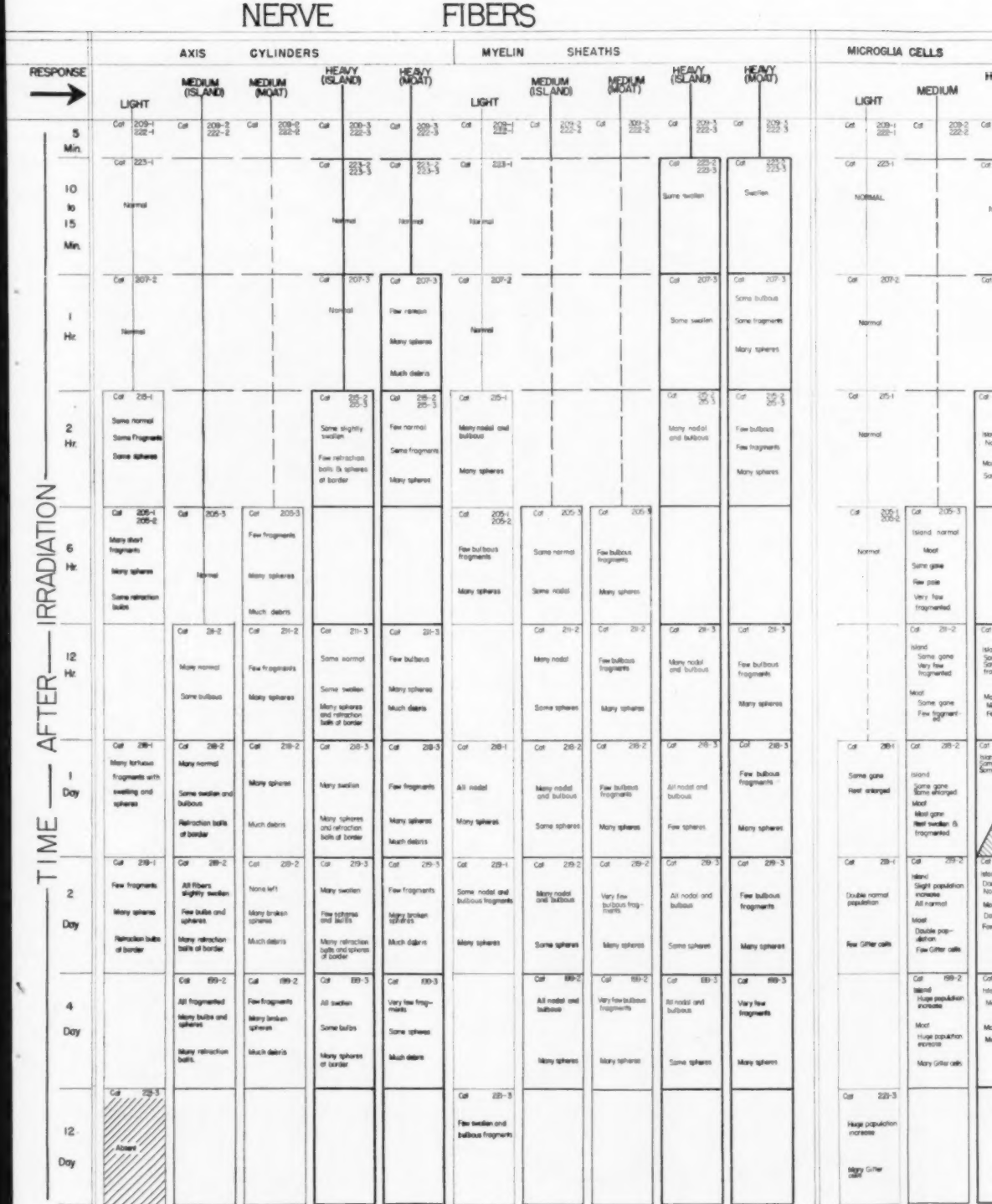
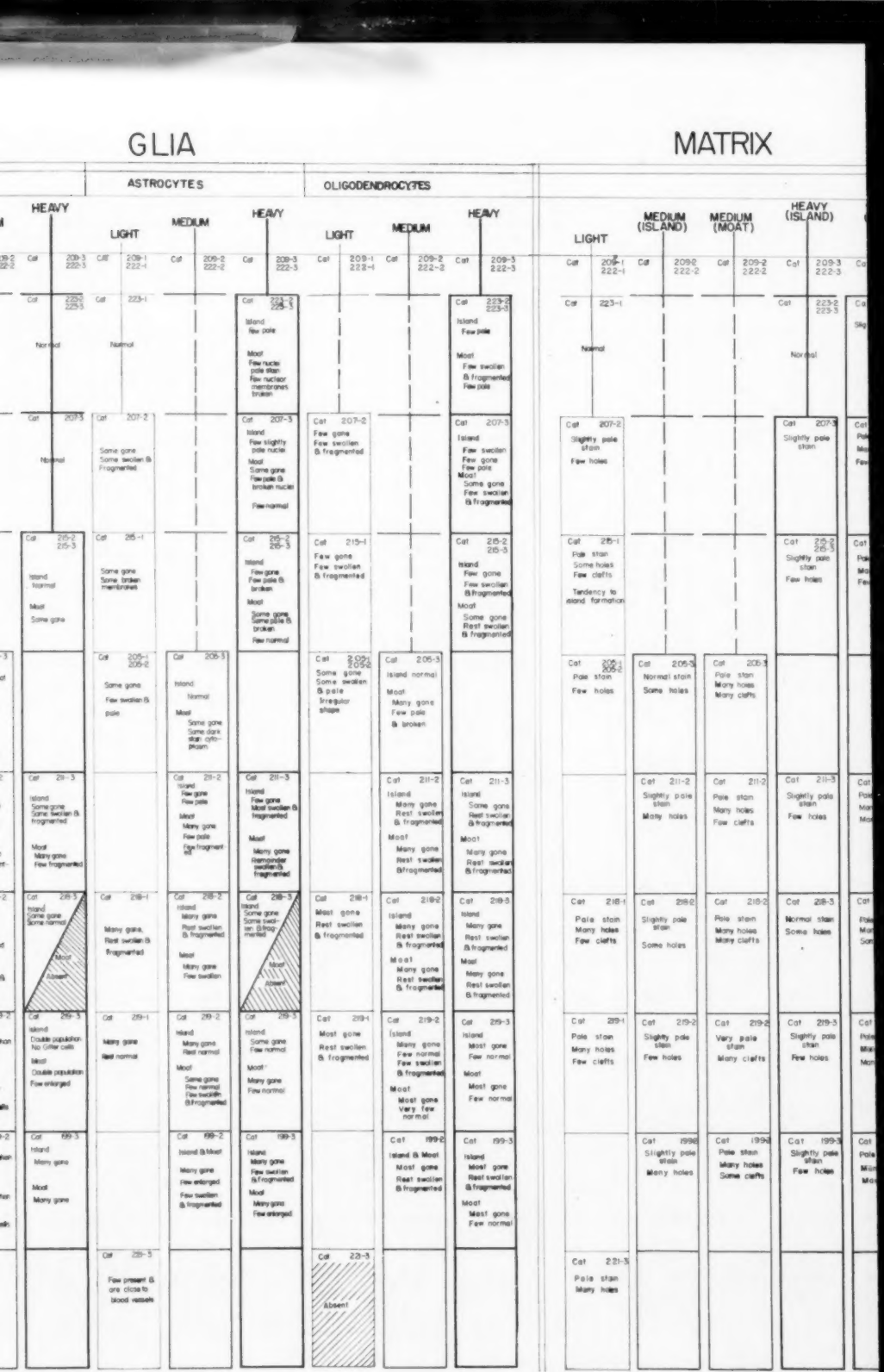


TABLE 3.—*Ultrasonic Le*



ic Lesions in White Matter: Histological Changes of Various Tissue Components as Function of Time After

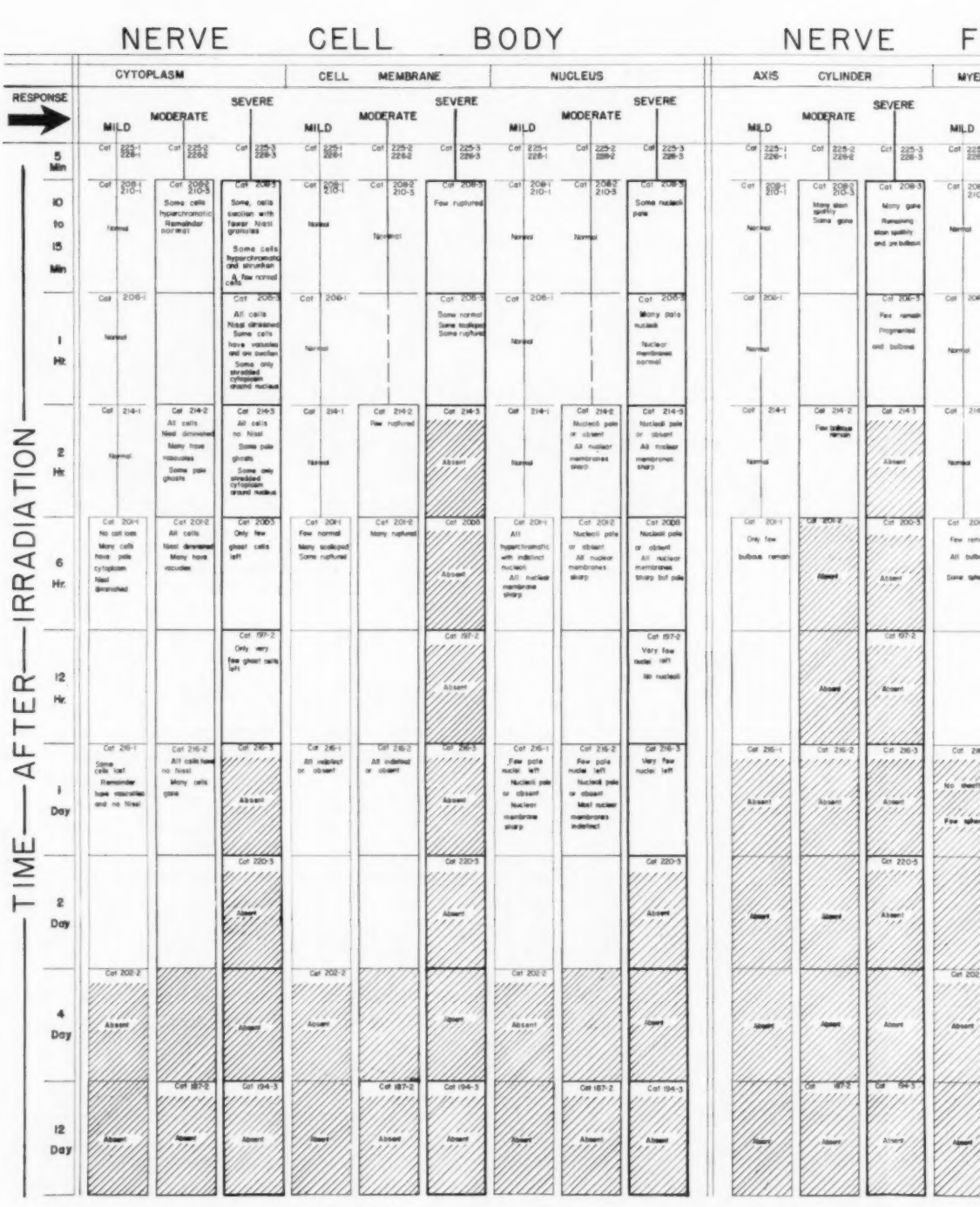
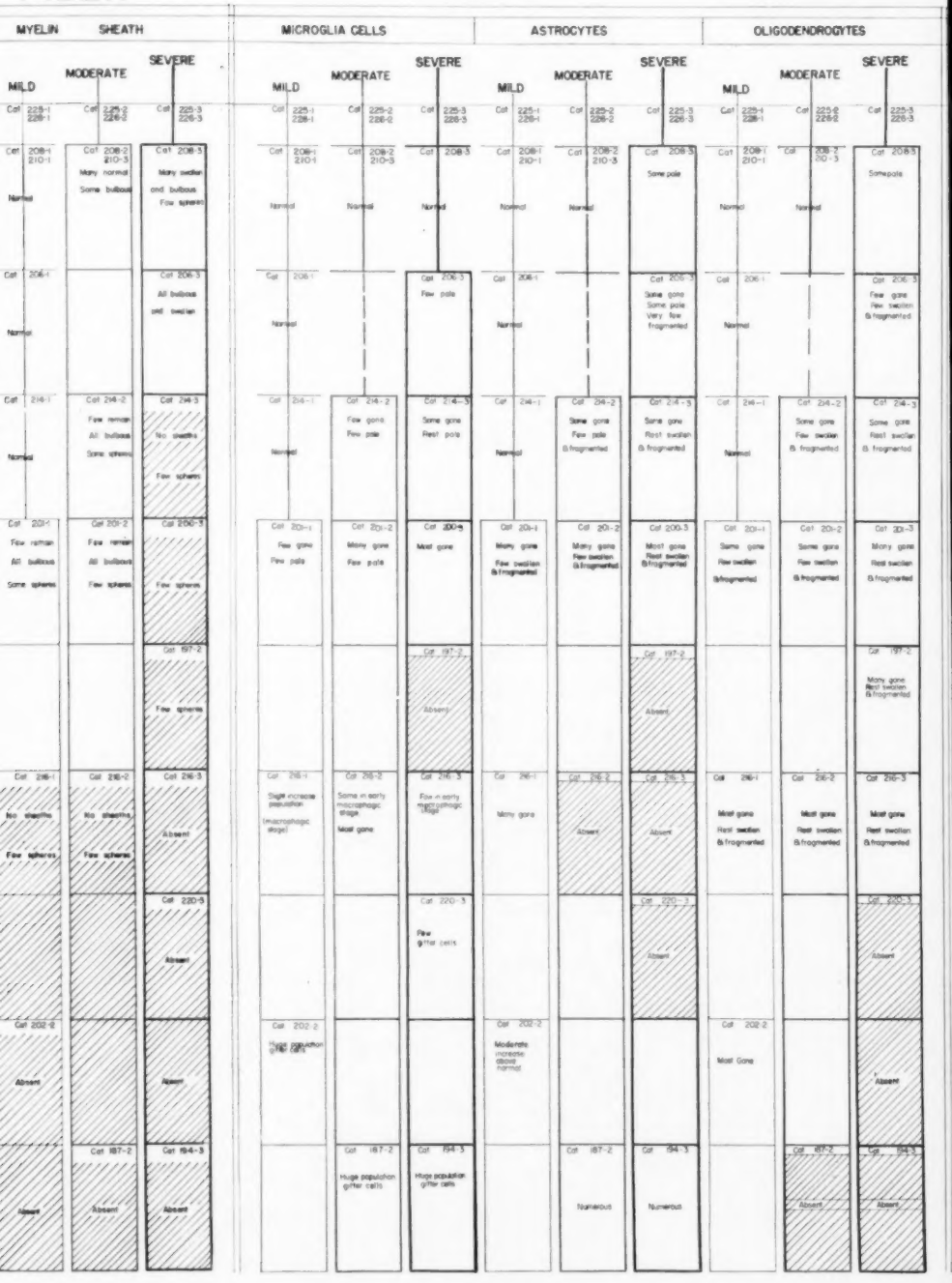
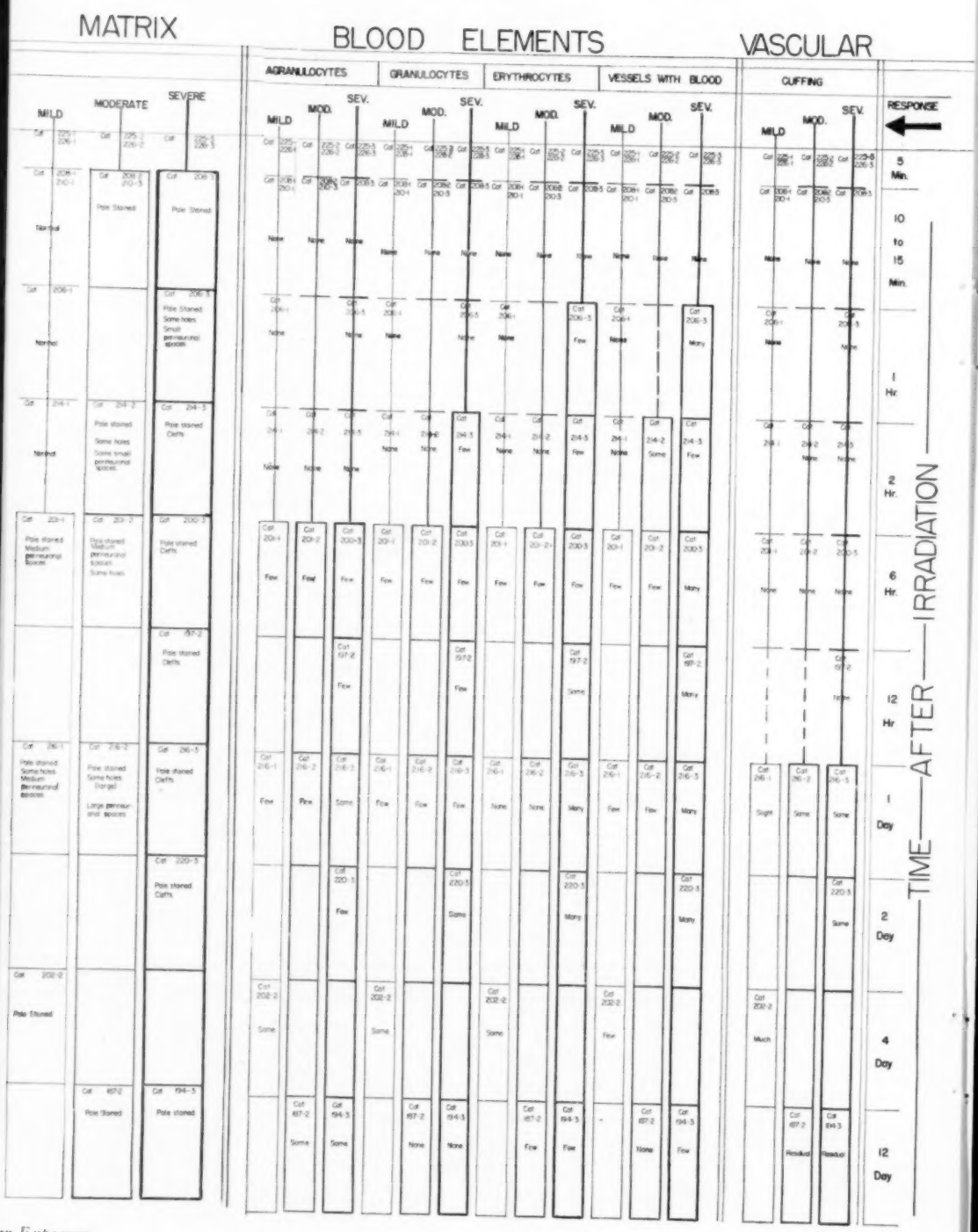


TABLE 4.—*Ultra*



-Ultrasonic Lesions in Gray Matter: Histological Changes of Various Tissue Components as Function of Time Aft


MATRIX
BLOOD ELEMENTS
VASCULAR
AGRANULOCYTES
GRANULOCYTES
ERYTHROCYTES
VESSELS WITH BLOOD
CUFFING
MILD
MODERATE
SEVERE
MOD.
SEV.
RESPONSE
5 Min.
10 to 15 Min.
1 Hr.
2 Hr.
6 Hr.
12 Hr
1 Day
2 Day
4 Day
12 Day
TIME — AFTER — IRRADIATION

er Exposure

these heavy lesions, which directly encroach on the adjacent gray matter, nerve cells and fibers are directly involved, as described in the section of this paper devoted to lesions of gray matter. A secondary effect on gray matter may follow the production of a lesion initially completely restricted to white matter. Fluid accumulations in the moat of the white-matter lesion might cause an edematous condition in the adjacent cortical gray matter which could be sufficient to destroy a few of the closer nerve cells. However, it is felt that changes resulting from this factor cause only reversible changes in the gray matter.

Effects of Ultrasound on the Gray Matter of the Cerebrum

The amplitudes of the acoustic pressure and particle velocity used to produce gray-matter lesions (Tables 2 and 4 and Figs. 11-13) were approximately the same as those for white matter, but the duration of the irradiation necessary to produce a lesion (at the intensities used) is one and one-half to two times as long.

The lesions produced in gray matter by ultrasound, and described in this paper, are classified as mild, moderate, or severe. It has not been possible, during the course of this investigation, to formulate criteria for the classification of gray-matter lesions which can be as readily applied as those formulated for the classification of white-matter lesions. In fact, the assigning of a gray-matter lesion to a particular class is decided primarily on a comparative basis. This method has the disadvantage that, given an arbitrary single lesion, it is difficult to assign it to a class without having available either a graded series of lesions with which to compare it or a detailed description of such a series. However, the comparative method does constitute a consistent one, as shown by Table 4.

It is possible, however, to formulate a few brief criteria which permit a rough assignment of a lesion to a class without using the comparative method. At 10 to 15 minutes after exposure a mild lesion is not seen histologically. A moderate lesion in this same time interval appears macroscopically as a uniform light-staining area, and a severe lesion exhibits a pale-staining band (moat) enclosing a central, darker-staining area (island). This island-moat formation is similar to that characteristic of medium and heavy white-matter lesions. From one hour to several days after irradiation mild lesions exhibit some holes as large as 150μ in diameter. In moderate lesions the density of the holes is high, and some as large as 500μ are present. Severe lesions are characterized by the presence of large, irregular, connected clear spaces. After the glial response is well developed (one to two weeks after irradiation), it is difficult to formulate even rough, noncomparative criteria of classification. A simply applied comparative criterion at these later stages is the relative size of the lesion (for single, isolated spot irradiations). As in the classification of white-matter lesions, the categories are arbitrary subdivisions in a continuous series.

Early Changes.—Two cats irradiated at a total of six positions (single isolated shots) were killed and perfused from six to eight minutes after exposure to ultrasound. None of the irradiated tissues shows any histological change, although serial sections were carefully examined for signs of a lesion. Animals killed and perfused from 10 to 16 minutes after irradiation show microscopically visible lesions.

At 10 to 16 minutes these lesions are characterized by a slightly pale-staining background in the moderate response. In the severe lesion (Fig. 11*C*), a pale-staining region surrounds a normal-staining central region (island). The perivascular spaces are slightly enlarged, but no blood cells are present in the vessels or in the tissue matrix of these perfused cat brains either in normal or in irradiated areas.

In severe lesions 10 to 15 minutes after irradiation some nerve cells are swollen and show diminution of Nissl granules and a general lack of staining ability of all parts of the cell. A few normal-appearing cells are still present in the lesion area. In mod-

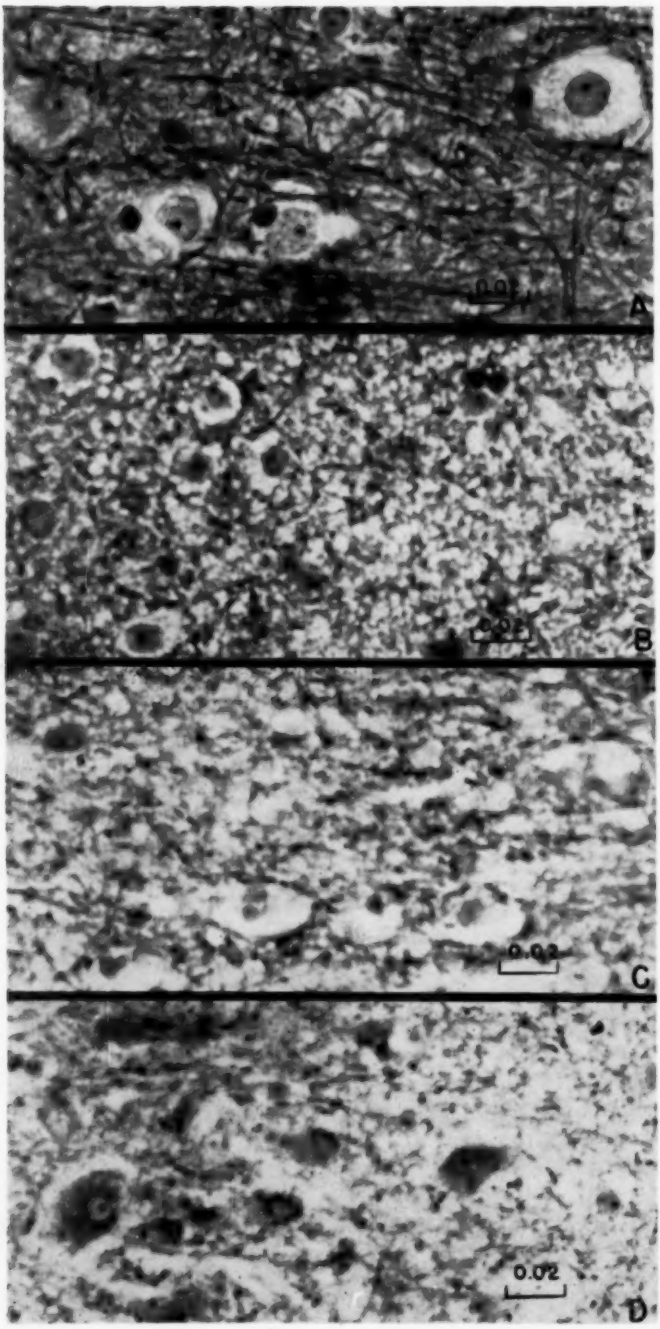
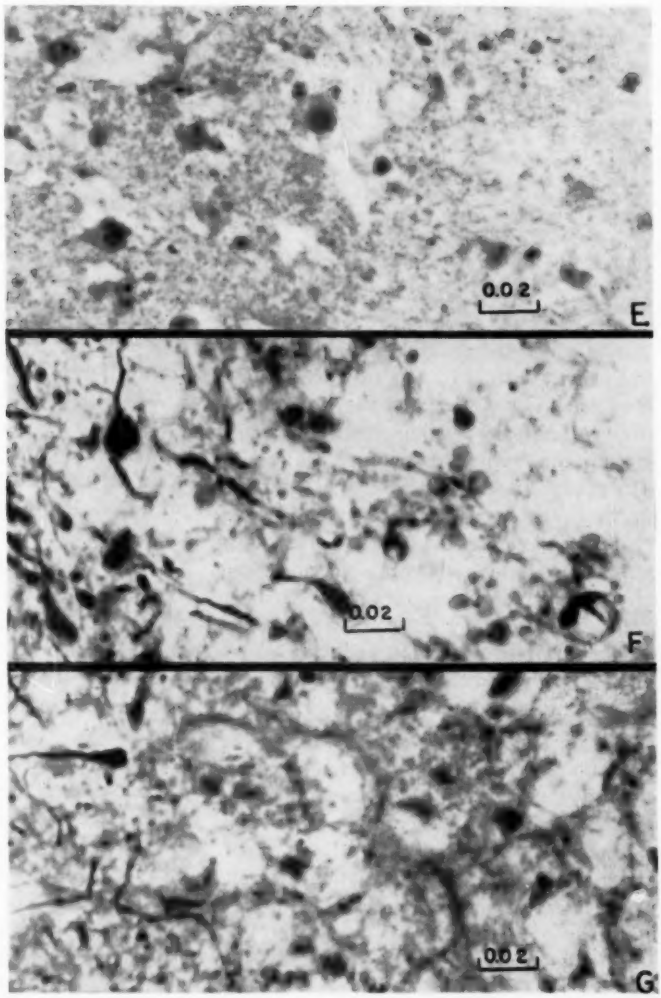


Fig. 13. — Stages of neuron degeneration in the cortical gray matter of a cat brain following ultrasonic irradiation; Romanes silver method; scale units in millimeters. *A*, normal cortical gray matter; *B*, spottily stained axis cylinders 10 minutes after irradiation; *C*, fragmentation of axis cylinders—early stage; *D*, granular cytoplasm in nerve cell bodies, fragments of axis cylinders, and small holes in the



matrix; *E*, debris of axis cylinders, free nerve cell nuclei with shreads of cytoplasm and holes in matrix; *F*, border zone of lesion, showing retraction bulbs, with large clear spaces and absence of distinguishable neural or glial components in adjacent region of lesion; *G*, border zone of lesion, showing retraction bulbs and adjacent region with glial scar (12 days after irradiation).

erate lesions early chromatolysis is observed in some nerve cells. Many of the myelin sheaths are still normal 10 minutes after exposure, but some appear bulbous. The axis cylinders stain spottily. However, in severe lesions many myelin sheaths are swollen and bulbous, and some spheres are present. Many axis cylinders are fragmented into dust-like granules, and the remainder stain spottily.

In a moderate lesion minimal changes appear in the nuclei of astrocytes and oligodendrocytes, but all microglial nuclei appear normal. The glia cells in a severe lesion appear normal with the exception of some pale-staining nuclei of astrocytes and oligodendrocytes and a few pale-staining microglial nuclei.

The next stage described is that of cats killed six hours after irradiation. This interval is chosen because it exhibits a spectrum of alterations from initial stages of chromatolysis, in the mild lesions, to virtual absence of cells, in the severe lesions.

The density of hyperchromatic nerve cells bordering the lesion is greater than in nor-

mal cortex. Such hyperchromatic cells can be seen, bordering gray-matter lesions, as late as one day after irradiation.

Six-Hour Lesions.—The background matrix is pale-staining in all lesions six hours after irradiation, and perineuronal spaces (clear spaces between the neuronal membranes and surrounding tissue structures) appear. The severe response shows, in addition to the above-described matrix changes, clefts in the tissue (Fig. 12).

The nerve cell bodies in the mild response exhibit a reduced amount of Nissl substance in the cytoplasm. In a few instances the cell membrane is ruptured and the cytoplasm is present only as a stringy material among large clear vacuoles around the nucleus. The nuclei are hyperchromatic, and the nucleoli are somewhat indistinct. In the moderate response, some cells have disappeared, no normal ones are seen, and many of the remainder have ruptured cell membranes and indistinct nucleoli. In the severe lesions the few remaining cells are ghost-like. A few isolated nuclei containing indistinct nucleoli and surrounded by faint shreds of cytoplasm remain.

Sections prepared with Romanes' silver stain show neurons with reddened cytoplasm, which progressively develop granulation, followed by rupture of the cellular membrane (Fig. 13*D*). The population of granules decreases, and free nuclei surrounded by a few of these particles are seen (Fig. 13*E*). The nucleolus next becomes pale, and finally the remnants of the original neuron are reduced completely to dust-like particles.

Axis cylinders are greatly diminished in number in the mild six-hour lesions and are absent in the moderate and severe lesions. In mild lesions the few fragments remaining are bulbous (Fig. 13*D*), and isolated spheres can be seen. The few remaining myelin sheaths in the mild lesions are bulbous, but only a few spheres remain in the moderate and severe lesions.

Many of the blood vessels are filled with blood cells in the severe lesions, although the brain was perfused and no filled vessels are present in the normal parts of the brain. Examination shows that this does not represent complete stasis, because the vessels are clear at later stages. The vessel walls at six hours are intact, and only a few scattered leucocytes and erythrocytes are found in the tissue matrix. The mild and moderate lesions contain only a few filled blood vessels, and few blood cells are present in the tissue spaces. The microglia cells are reduced in numbers in all lesions. The astrocytes and oligodendrocytes are also reduced numerically, those remaining being pale, swollen, and fragmented.

Later Changes.—The remainder of this section of the paper consists of separate accounts of the sequential changes which occur in the individual tissue components, presented in the following order: matrix, nerve cells, nerve fibers, glia, and blood vessels and blood cells.

Matrix: The pale-staining background appears as early as 10 minutes after irradiation in moderate and severe lesions. It is accompanied by the appearance of small perineuronal spaces. One hour after exposure small holes containing clear fluid have appeared in the tissue (Fig. 13*C*). Two hours after exposure, in the severe lesions, this fluid is present in the form of clefts in the matrix (Fig. 12). Mild responses are evident histologically six hours after irradiation by the presence of perineuronal spaces and a lighter-staining background. The perineuronal spaces and fluid-filled holes and clefts become larger and at one and two days after irradiation are quite prominent (Fig. 13*F*). At later stages (12 days after exposure), when the lesion area becomes densely populated with glia cells, these spaces are no longer present (Fig. 13*G*).

Nerve Cells: The nerve cells, as indicated previously, show no histological changes within 5 to 8 minutes, but 10 minutes after irradiation definite changes appear. Hyperchromatism, paleness, and chromatolysis are all apparent 10 to 15 minutes after exposure. These cellular changes are succeeded rapidly by advanced chromatolysis, granulation of

the cytoplasm (Fig. 13*D*), and liquefaction (Fig. 13*F*). Six hours after irradiation only a few ghost cells are left in severe lesions, and at one day all cells have disappeared. In mild lesions cellular effects do not become apparent until six hours; by one day some cells are left, but presumably these will quickly disappear, since at four days no nerve cells are present in any of the lesions.

The nuclei and nucleoli exhibit a series of changes which accompany the cytoplasmic ones. The nucleus stains more darkly, but persists with its membrane, and is the last part of the nerve cell to lose its morphological appearance (Fig. 13*E*). The nucleolus becomes indistinct and unstainable before the remainder of the nucleus disappears. The cellular changes are similar to those described by Nissl, Spielmeyer, and Bielschowsky except that here the rate of dissolution is somewhat faster. The changes herein described are not pathognomonic for ultrasound but are characteristic of nerve cells undergoing rapid destruction.

Nerve Fibers: Ultrasound initiates the early stages of breakdown in the axis cylinders and myelin sheaths of the cortical gray matter faster than it starts them in the subcortical white-matter lesions. Axis cylinders show early changes in the 10- to 16-minute lesions (Fig. 13*B*) and have completely disappeared 2 hours after irradiation in the severe lesions (Fig. 13*E*). In mild lesions the first sign of pathological response is at six hours, and the fibers and their myelin sheaths are lost one day after exposure. The greater speed with which the breakdown products of the fibers are removed from gray-matter lesions than from white-matter lesions may be related to the relatively small amount of fiber debris to be handled in the gray-matter lesions, as compared with the large amount of fiber wreckage in the white-matter lesions. The greater vascularity of the gray matter may also be important in this regard. The disintegration of the individual nerve fibers is similar to that seen in the white-matter lesions except for the altered time course.

Glia: A few of the microglia cells react by becoming paler-staining 1 hour after irradiation in the severe lesions; by 6 hours most are absent from the lesion area, and at 12 hours all have disappeared. At one day they are returning to the lesion and beginning to metamorphose, so that by two days they are fully developed as "gitter," or fat-granule, cells. (The density is approximately equal to that of the normal population of microglia cells.) By 12 days their number has increased enormously and they dominate the field of the lesion. In moderate lesions they never entirely disappear and at one day exhibit metamorphic changes. By 12 days the gitter cells are very numerous, as in the severe lesion. In mild lesions only a few disappear; at one day the population (macrophagic stage) has doubled, and at four days these cells are present in large numbers.

The astrocytes react early (10 to 15 minutes after irradiation) by staining less intensely, and 12 hours after exposure all have disappeared from the severe lesions. In the moderate lesions they are absent at the one-day stage. In both grades of lesions they are numerous at 12 days. In the mild lesions they are reduced in number by six hours, but at four days their population has increased above normal.

The oligodendrocytes are reduced to about one-half their number at two hours in the moderate and severe lesions. Many of the remaining cells are hyperchromatic (also shrunken). By two days all are absent in the severe lesion. At four days most have disappeared from even the mild lesion, and at 12 days none are present in the center of any lesion.

Blood Vessels and Blood Cells: At 10 to 15 minutes after irradiation all blood vessels are cleared of blood elements by the perfusion. At one hour, however, many of the vessels in the severe lesion have blood cells in them, in spite of the perfusion, which has emptied all other vessels in the normal tissue. The presence of these blood cells may possibly be explained by hemoconcentration,

or even sludging of the blood. However, the absence of obvious volume changes in the irradiated tissue should be considered in postulating any such mechanism. In any event, many such vessels are found only in some severe lesions; others contain only a few such filled vessels. The moderate lesions never have as many filled vessels, and the mild lesions have only a few filled blood vessels. There are more erythrocytes outside the vessel walls in lesions which have many filled vessels, and fewer of them in lesions containing only a few blood-filled vessels. In general the erythrocytes free in the tissues reach their numerical peak at the first and second days in the severe lesions. In these instances there are occasional clumps of erythrocytes of 50 to 100 cells in a section. In the moderate and mild lesions only scattered red cells are seen, and an occasional small cluster of a dozen cells. A few granulocytes and agranulocytes make their appearance at six hours, and some are still present at four days.

Perivascular cuffing is just perceptible at one day, but is easily seen at two to four days, and consists of a row or two of cells around the vessels. It is more prominent at the periphery of the lesions. At 12 days only slight, residual cuffing is present. This response is not nearly as marked as reported elsewhere [2] in larger, multishot white-matter lesions.

COMMENT

High-level (acoustic pressure and particle velocity) ultrasound can be used to produce selective lesions, restricted to a few cubic millimeters of tissue if desired, in either the white or the gray matter of the brain. Lesions can be made of any desired larger size, as reported earlier,* by the simple expedient of using multiple overlapping shots. The ability to place such lesions deep within the substance of the brain without interfering with any of the intervening tissue is a powerful method in both experimental neurology and clinical neurosurgery.

The dosage of ultrasound necessary to produce irreversible changes in white matter is less than that required to change gray matter; consequently, it is possible to interrupt fiber tracts without destroying neighboring or surrounding gray matter. Such selectivity in conjunction with the absence of interruption of the vascular system finds immediate application to a variety of neurological problems.

When a tissue component is irreversibly affected by the ultrasound, the consequent degenerative changes are not specific to the ultrasonic method. Similar changes occur in response to other agents, although the speed of breakdown may be different. Of course, as a result of the selective action on specific tissue components, the over-all pattern of breakdown may be considerably different.

The ultrasonically irradiated tissue exhibits no long-delayed responses, such as those observed following conventional and high-energy x-irradiation † and high-energy deuteron irradiation.[14]

The preservation, for several days after irradiation, of an almost normal appearance of the nerve fibers in the islands of the medium and heavy white-matter lesions reminds one of some observations of Cajal.[9] This investigator produced "preserved" fibers by isolating blocks of nerve tissue by knife cuts. It was Cajal's opinion that the immediate "death" of the nerve elements in his experiments was caused by contusion, tension, or compression. If brain tissue was cut with a sharp knife, as contrasted with the use of a dull instrument, and, consequently, the tension and compression stresses minimized, only a few "preserved" fibers were produced.

The island-moat structure of ultrasonically produced lesions might possibly be elucidated as follows: In mild lesions the chemical changes are less drastic than in centers of the medium and heavy lesions, and, consequently, the tissue is capable of autolysis. This is also true of the moats of these latter lesions. The islands of the medium and

* References 1 and 2.

† References 12 and 13.

heavy ultrasonic lesions experience more pronounced chemical changes and, subsequently, lack the inherent ability to alter their morphological appearance.

At dosage levels which produce lesions in either white or gray matter the blood vessels remain intact and reveal no hemorrhages. At higher doses (roughly twice the duration of the threshold dose for gray-matter lesions, at the sound level used in this study) a vessel is occasionally broken and a small hemorrhage produced. However, at doses which are sufficient to produce complete destruction of nerve tissue no vessels are broken.

No obvious swelling of the lesion area occurs (as evidenced by absence of compression in surrounding tissue), although some small amount of fluid may be transported by the vascular system to the region. The holes and clefts which appear in the matrix as the tissue undergoes dissolution may result almost entirely from autolysis and liquefaction. The extravasations of erythrocytes may result from vascular embarrassment caused by the extensive tissue necrosis.

Many of the gray-matter lesions contain a number of blood-filled vessels which resist perfusion (at the pressures used) in animals killed from one hour to four days after irradiation. These vessels are intact, and it is possible that the blood elements remain in them because of increased impedance to circulation caused by hemoconcentration and altered pressure conditions in the necrotic tissue.

The physical mechanism of the action of ultrasound to produce tissue damage (of the type reported herein) in the central nervous system is not yet understood. Although it is not felt that heating is the principal factor, it certainly is important, because the primary process is temperature-dependent. As described in an earlier paper, sound is absorbed at almost twice the time rate (for equal acoustic intensities) in white matter as in gray matter, so that this property must be considered in any analysis of the differences in ultrasonic doses required to produce lesions in gray matter as compared with white matter. It is specifically noted that single myelinated fibers in the gray matter are not affected at ultrasonic doses which produce lesions consistently in the white matter, i. e., in masses of myelinated fibers. That heat is not the principal factor acting to produce the changes in the tissue is shown by experiments on frogs and newborn mice. These animals, whose body temperatures are lowered before and during irradiation, have lesions produced in their nervous systems by ultrasound even though the peak temperatures reached during irradiation are well within the physiological limits for the animal. The work on frogs has been reported elsewhere,[15] and that on mice is currently in progress.

The phenomenon of cavitation in an intense sound field, i. e., the growth of cavities from gas nuclei, with consequent tearing of the tissue fabric, can probably be eliminated as a factor in the production of lesions in the experiments reported here, since no animals show any tissue disturbance until at least 10 minutes after irradiation. Careful examination under the microscope of stained sections of irradiated regions fixed at less than 10 minutes after exposure fail to reveal any changes. Cavitation tears in the tissue would show immediately. Additional evidence that cavitation does not contribute to the mechanism is forthcoming from previous frog experiments, as shown by the fact that irradiation under hydrostatic pressure [15] sufficiently high to prevent cavitation completely does not eliminate the effect of the ultrasound on the tissue.

Two lesions, 4 days and 12 days after irradiation, exhibit normal-appearing axis cylinders in silver stains; yet in the Weil stain these same fibers show no trace of a myelin sheath. The nerve cell bodies are absent, as in other lesions, at these survival times. These lesions appear to be minimal, i. e., close to the ultrasonic dose threshold necessary to produce a histological change. These axis cylinders do not resemble the

"preserved" fibers previously discussed in this paper, because they appear normal along their entire length, including the portion in the border zone of the lesion. In addition, these naked axis cylinders occur in the minimal lesion, whereas the "preserved" fibers in white-matter lesions are found most abundantly and longest preserved in the heavy response. Apparently, a demyelinating process is operative, and the axis cylinders may be alive rather than preserved. Regeneration, as reported by Windle and Chambers [10] in the spinal cord of the cat, does not appear probable, considering the normal pattern and abundance of the fibers. The short survival times of the animals after exposure (4 and 12 days) precludes such complete regrowth. Further study of these minimal lesions is planned, with the intention of comparing them with the demyelination occurring in certain pathological conditions.

SUMMARY

High-level (acoustic particle velocities of the order of $5[10]^8$ cm/sec. and pressure amplitudes of the order of 50 atmospheres), focused ultrasound (frequency 980 kc.) can produce selective lesions in either the gray or the white matter of the brain. The following characteristics of such lesions are of special interest:

1. The volume of affected tissue can be kept small in size (a few cubic millimeters). Larger regions can be affected by moving the focal spot of the beam around.

2. A lesion in the depths of the brain can be produced without affecting any intervening tissue.

3. The doses of ultrasound necessary to produce irreversible changes in gray matter are higher than those required for a white-matter lesion (at 50 atmospheres pressure amplitude and $5[10]^8$ cm/sec. particle velocity amplitude the minimal durations are in the ratio of about 2:1). This means that fiber tracts can be interrupted without disturbance to neighboring or surrounding gray matter.

4. In the white matter the tissue components exhibit the following order of susceptibility to change by sound: myelin sheaths, axis cylinders, glia, and blood vessels. In the gray matter the same order is preserved, with the addition that the nerve cell bodies are about as sensitive as the axis cylinders. The blood vessels are the most resistant tissue in the brain to the action of the sound. At doses which induce minimal histological changes an apparent demyelination can be accomplished without morphological change of the axis cylinders.

5. Ultrasonic radiation does not produce long-delayed effects, such as are seen in tissue irradiated with x-rays.

Dr. Rolfs Krumins contributed extensively to the study of the glial response, as reported in this paper.

REFERENCES

1. Fry, W. J.; Mosberg, W. H.; Barnard, J. W., and Fry, F. J.: Production of Focal Destructive Lesions in the Central Nervous System with Ultrasound, J. Neurosurg. **11**:471, 1954.

2. Barnard, J. W.; Fry, W. J.; Fry, F. J., and Krumins, R. F.: Effects of High Intensity Ultrasound on the Central Nervous System of the Cat, J. Comp. Neurol., to be published.

3. Fry, W. J.; Barnard, J. W.; Fry, F. J.; Krumins, R. F., and Brennan, J. F.: Ultrasonic Lesions in the Mammalian Central Nervous System, Science **122**:517, 1955.

4. Fry, W. J., and Fry, R. B.: Determination of Absolute Sound Levels and Acoustic Absorption Coefficients by Thermocouple Probes—Experiment, J. Acoust. Soc. America **26**:311, 1954.

5. Heyck, H.: Ultraschall und Zentralnervensystem, Schweiz. med. Wchnschr. **82**:97, 1952.

6. Heyck, H., and Höpker, W.: Hirnveränderungen bei der Ratte durch Ultraschall, Monatsschr. Psychiat. u. Neurol. **123**:42, 1952.

7. Lindstrom, P. A.: Prefrontal Ultrasonic Irradiation—a Substitute for Lobotomy, A. M. A. Arch. Neurol. & Psychiat. **72**:399, 1954.

8. Lynn, J. G., and Putnam, T. J.: Histology of Cerebral Lesions Produced by Focused Ultrasound, Am. J. Path. **20**:637, 1944.

9. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, Oxford University Press, 1928.

10. Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932.

11. del Rio Hortega, P., and Penfield, W.: Cerebral Cicatrix: The Reaction of Neuroglia and Microglia to Brain Wounds, Bull. Johns Hopkins Hosp. **41**:278, 1927.

12. Arnold, A.; Bailey, P., and Laughlin, J. S.: Effects of Betatron Radiations on the Brains of Primates, Neurology **4**:165, 1954.

13. Clemente, C. D., and Holst, E. A.: Pathological Changes in Neurons, Neuroglia and Blood-Brain Barrier Induced by X-Irradiation of Heads of Monkeys, A. M. A. Arch. Neurol. & Psychiat. **71**: 66, 1954.

14. Tobias, C. A.; Van Dyke, D. C.; Simpson, M. E.; Anger, H. O.; Huff, R. L., and Koneff, A. A.: Irradiation of the Pituitary of the Rat with High Energy Deuterons, Am. J. Roentgenol. **72**:1, 1954.

15. Fry, W. J.; Tucker, D.; Fry, F. J., and Wulff, V. J.: Physical Factors Involved in Ultrasonically Induced Changes in Living Systems: II. Amplitude Duration Relations and the Effect of Hydrostatic Pressure for Nerve Tissue, J. Acoust. Soc. America **23**:364, 1951.

16. Windle, W. F., and Chambers, W. W.: Regeneration in the Spinal Cord of the Cat and Dog, J. Comp. Neurol. **93**:241, 1950.

Procaine Oil Blocking of the Globus Pallidus

H. NARABAYASHI, M.D.
T. OKUMA, M.D.
and
S. SHIKIBA, M.D., Tokyo

In about six years' use of the stereotactic operation in this laboratory, during which the first, second, and third models of the stereoencephalotome were completed, our main concern has been the globus pallidus and the thalamus. Several reports have previously been published on the technique used and the earlier results.

In this paper, the treatment of rigidity and tremor of Parkinsonism, using a stereotactic injection of procaine HCl in oil and wax, will be described and discussed. We believe that stereoencephalotomy, in addition to the opportunities for treatment that it offers, provides an approach to an investigation of the function of the subcortical ganglia.

Since James Parkinson described paralysis agitans (Parkinson's disease) as a senile disorder in 1817, the neuropathology of this disease has been studied by many investigators. At first this disease was thought of as a senile process for which a hereditary predisposition was assumed. But after the encephalitis epidemic at the end of the World War I similar symptoms were observed as residuals. This new disorder was called postencephalitic Parkinsonism. These two groups of similar symptoms were considered at first to be different in etiology and neuropathology. Paralysis agitans was differentiated from postencephalitic Parkinsonism as usually beginning in the senile or presenile period and as having as main symptoms the characteristic tremor, motor disturbances with less rigidity, less pronounced vegetative symptoms, and fewer pupillary disturbances. But, with increasing experience, it became clear that cases for which the differentiation seemed to be impossible were not rare.

As to the neuropathology of these diseases, Goldstein first showed (1922) that in the cases of postencephalitic Parkinsonism the substantia nigra was selectively affected and that nerve cells of this nucleus were degenerated. Many similar findings were reported in the following 10 years. Although Holzer and others produced evidence that the globus pallidus, corpus striatum, and thalamus were also involved, Tretiakoff, Lhermitte, Cornil, Spatz, Hassler, and Klaue agreed that the substantia nigra was chiefly affected, and that the globus pallidus was affected to a far slighter degree.

In paralysis agitans the classical work of Lewy and Holzer demonstrated the main site of the pathological process to be in the globus pallidus. On the contrary, Tretiakoff, Foix, Nicolesco, Hassler, and others believed that the pathological changes were more marked and constant in the substantia nigra.

Governing opinions at present are that this nucleus is the key to the pathology in both groups of diseases. In view of these opinions and clinical experiences, Spatz believed paralysis agitans to be a more slowly progressive, less manifest, sporadically occurring senile type of postencephalitic Parkinsonism, and Klaue supported this opinion by a symptomatologic and neuropathological analysis of his 100 cases. But it is still unknown how degeneration of this nucleus causes rigidity and tremor. This must not be forgotten when we try to find evidence supporting the theory of the suppressor system in explanation of the mechanism of tremor.

Received for publication April 12, 1955.

From the Department of Neurology and Psychiatry, Tokyo University School of Medicine.

SURVEY OF THE SURGICAL TREATMENT OF PARKINSONISM

Any treatment of Parkinsonism remains symptomatic, since the etiology and pathological physiology remain obscure. Most commonly employed are antispasmodic alkaloids (atropine, scopolamine) and compounds (mephenesin [Myanesin], caramiphen [Parpanit], trihexyphenidyl [Artane], and antihistamine compounds). These medicaments are more useful for decreasing muscle rigidity than for relieving tremor. Moreover, these chemicals have side-effects, i. e., dizziness, thirst, photophobia, palpitation, and gastrointestinal disturbances. For these reasons, new treatments, including chemotherapy and neuro-surgery, are being tried.

In the past 10 years various neurosurgical procedures for the hyperkinetic disorders have been employed with the aim of controlling the hyperkinetic movement. Most of these procedures are based on the theory of the suppressor system and of the parapyramidal system, introduced by Papez, Bucy, Browder, Meyers, and others. The suppressor system is believed to include Areas 4s, 6, and 8 of the precentral region, the descending fibers from these areas to the caudate nucleus, putamen and globus pallidus, and the thalamic nuclei, and ascending fibers from these nuclei to the motor and premotor cortex. Electrical stimulation of Area 4s inhibits other cortical activity and hyperkinetic movements, so that this system has been called the suppressor system. In explaining Parkinsonian tremor, the substantia nigra is also considered to play an important role in neural suppression. Hyperkinetic movements are considered manifestations of the functional confusion, caused by some pathological process within the system. Surgical destruction of certain parts of the system is thought to reestablish some functional balance within the system. Though this idea is still hypothetical, and unproved, many operations based on it have been attempted. Fiber connections of the above areas and nuclei are known, and an intimate correlation of these parts must be assumed. But we can say nothing about how one part interacts with others, i. e., the functional mechanisms within the suppressor system. Electrical stimulation of any one point in the system does not cause the hyperkinetic movement itself.

Meyers and Wyke sectioned U-fibers connecting motor and premotor areas for relief of Parkinsonian tremor, supposing that these fibers may transmit controlling impulses from the premotor to the motor area; this operation, however, was not followed by other investigators because of its serious side-effect, palsy. Klemme reported, also, that resection of the premotor area relieved tremor in his 200 cases. Bucy and Case resected the left premotor arm area in a post-traumatic case with right-sided tremor. After the resection, marked, but transient, paralysis of the extremity appeared. They concluded that resection of Areas 4 and 6 was necessary to abolish tremor, though it may produce severer palsy.

Bucy and Buchanan, in athetosis, and Takebayashi, in many kinds of hyperkinetic movements, reported on corticolysis, i. e., subcortical undercutting of the circumscribed motor and premotor areas. These procedures are analogous in concept, but different in the width of the area to be attacked. We believe that one must be cautious in employing this hypothesis as the basis for the practical operations. It was our own experience with six cases of corticolysis or cortical ablation restricted to Area 6 in treatment of choreoathetotic movements or tremor that improvement could be reached only to the degree to which the affected side was paralyzed.

CONCEPTION OF BLOCKING OF THE GLOBUS PALLIDUS

Since cortical undercutting is based on the highly questionable suppressor theory, other methods seem indicated. We reported previously the results of procaine-oil blocking of the globus pallidus in double athetosis. The procedure was based on the idea of the antagonistic functional correlation of the corpus striatum and the globus pallidus. The elimination of striatal control over the globus

pallidus by pathological processes was thought to produce choreoathetotic movements, as a release phenomenon. Jacob and Foerster originated this hypothesis. Thus, blocking of the globus pallidus was thought to suppress its released hyperactivity.

Our experience was that the athetotic movement was improved, but not abolished, by this operation. Observation suggested that the effect was dependent on a change in muscle tone, or that abnormal muscle tone might be a factor in producing unusual movements. Postoperatively involved muscles never reach the same level of tonic contraction seen preoperatively, change being followed by coincident symptomatic improvement.

Wilson and associates said that in the experimental animal stimulation of the globus pallidus did not produce a definite motor effect. Mettler and Ades reported that its stimulation had the effect of giving a plastic tonic base to cortically induced movement contralaterally.

From these experiences, we speculated that blocking of function of this nucleus might relieve clinical conditions characterized by muscle rigidity, i. e., Parkinsonism. In addition to such theoretical considerations, we were motivated to reexamine Meyers' operation on the caudate nucleus for tremor by use of the stereotactic method. He reported three cases in which the caudate nucleus was resected by suction following craniotomy and partial resection of the frontal lobe. This operation seemed to be effective for tremor. We thought that a much more selective invasion of the caudate nucleus would be possible with the stereotactic method than by such a major neurosurgical procedure. We decided to try this method cautiously on a patient with severe Parkinsonism, and, in order to get a reversible local narcotic effect, procaine hydrochloride in aqueous solution was chosen for injection.

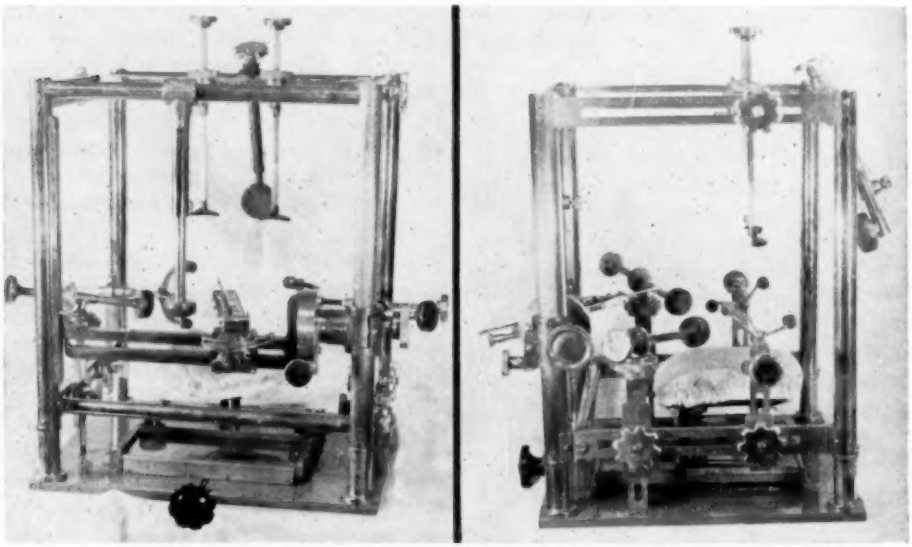


Fig. 1.—Third model of our stereoencephalotome for use in the supine position.

Several papers have appeared in the past four years on the stereotactic instrument and the technique of the operation used in this laboratory. Figure 1 shows the third model of the stereoencephalotome. Three coordinate planes—the horizontal, connecting the inferior ridge of the orbit and both external auditory poles; the vertical, passing through the external auditory pole and per-

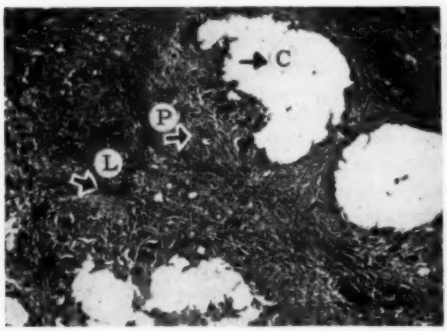
pendicular to the horizontal, and the midsagittal—are the standard planes of the instrument. The point of crossing of these three coordinate planes constitutes the zero point of our third model. After visualization of the third ventricle by pneumoencephalographic study, the position and coordinates of the globus pallidus can be measured. The authors found in six cadavers that this nucleus had almost the same horizontal and vertical coordinates as the massa intermedia.

Precise results from stereoencephalotomy in our laboratory have depended on two points: First, the points to be inserted were referred to the above-mentioned zero point of the three coordinate planes, and not to the pineal body. Second, all the operative procedures were performed with the patient in the supine, and not in the sitting position, because this permitted more stable fixation of the instrument to the skull.

It is not certain whether procaine HCl has an anesthetic effect on the central nervous system. Sasaki and Wake found that procaine and other local anesthetics of this group have amino radicals and benzene nuclei and commonly disturb myostatic function when absorbed. These chemicals have selective affinity for the basal ganglia, especially the substantia nigra and globus pallidus.

But this action is the so-called absorption effect, and not a local effect, when the chemicals are directly applied to brain tissue. Reports of direct application of procaine to brain tissue are few. Bailey and others blocked the frontal white fibers by injection of aqueous procaine in order to predict the effects of prefrontal lobotomy. Two cubic centimeters of 2% aqueous procaine HCl solution blocked function of the frontal lobe and demonstrated that injected procaine showed diffusion within 60 minutes. For this reason, we considered using procaine HCl in oil and wax to concentrate and prolong the local narcotic effect.

Fig. 2.—(*C*) Cavity of oil and wax mixture; (*L*) lymphatic infiltration; (*P*) proliferation of multinuclear giant cells.



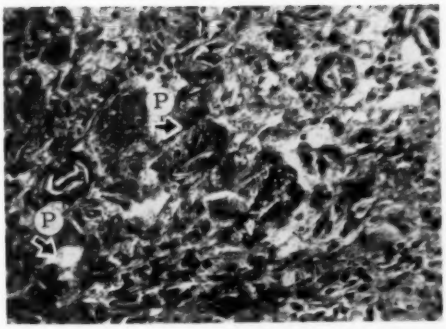


Fig. 3.—Proliferation of multinuclear giant cells (*P*).

The oil-and-wax mixture for injection into the brain tissue, through a 22 cm. needle (the internal diameter being 0.6 mm.), must have adequate viscosity for injection, and must not be so fluid as to return through the needle. Such a condition can be obtained by phase change depending on temperature. This temperature of changing phase should be near body temperature in order to avoid tissue thermocoagulation.

For this purpose, 10 series of mixtures of oil and wax in various percentages were examined, and a mixture of 90% oil and 10% procaine HCl was found to be best. It is semisolid at body tempearture and liquefies at 45 C.

Before this was used in the human brain, injections of six cats and two rabbits were done.

In the following report, the histological changes in a cat killed 76 days after injection of procaine in oil are described.

CAT 2.—A cat weighing 2.7 kg. had 0.3 cc. of procaine in oil injected into the area near the thalamus on April 7, 1952.

Macroscopically, there were found circumscribed round or oval collections of the injected oil. Oil and wax were removed in the process of alcohol fixation, with resulting cavities. Proliferation of multinuclear giant cells in the area was the most noticeable tissue reaction, particularly near the edge of the excavated cavities. Around these proliferations, granular-cell infiltration (or compound granular corpuscles) near and in the perivascular space was usually found. These cells contained phagocytosed hemosiderin, originating from the hemorrhage by diapedesis in the acute stage. Disseminated lymphocytic infiltration near the vessels was common. In the relatively distant white matter there was proliferation of hypertrophic macroglia cells, suggesting that injection influences a relatively wide area.

REPORT OF CASES

Of 60 cases in which we have operated, 26 selected cases of Parkinsonism will be reported here, as these had been observed for more than 18 months. The etiology of these cases was not always clear. However, Cases 5, 7, 9, 11, 12, 13, 14, and 20 were considered instances of paralysis agitans, and Cases 16, 19, and 21, postencephalitic, the other cases remaining obscure in nature.

Of 26 cases, 9 had unilateral involvement and 17 bilateral. Three had only tremor; 8, rigidity alone, and the other 15 had both rigidity and tremor, in various degrees. The cases are grouped according to symptoms, and of each group one or two representative cases will be described in detail. Other cases are briefly noted in the Table.

The grade of rigidity was measured in four degrees, proportional to the rate of the finger-touch test (rapid apposition of thumb to forefinger).

Grade	Finger-Touch Rate
4+	Less than 10/100 sec.
3+	20/100 sec.
2+	30/100 sec.
+	40/100 sec.

Tremor was 4 to 7 cps and was classified under four degrees, according to its amplitude and susceptibility to control by the patient.

In all cases findings were recorded in moving pictures before and after operation.

A. Both Rigidity and Tremor

Case 1 (Operation 1).—Man, aged 27, electrical engineer. Diagnosis: right-sided hemi-Parkinsonism.

This was the first human case we subjected to injection of the globus pallidus. The patient's symptoms first began in 1948 with slight tremor in his right arm, followed by rigidity. By 1952 the symptoms had progressed to a very marked degree in the right upper and lower extremities. The left side remained almost normal. There was no history of epidemic encephalitis and no suggestive family history. Atropine sulfate, scopolamine hydrobromide, and trihexyphenidyl had proved to be only partly effective. On admission, the patient had mask-like facies, slight disturbance of articulation, propulsive and shuffling gait, and bending posture. There was a right-sided vigorous tremor of relatively large amplitude and 3+ rigidity. The rate of finger touch was 15 per 10 seconds and, correspondingly, voluntary movements, writing, eating, and dressing were difficult. Diadokokinesis and the motion of swinging his right arm during walking were almost impossible.

Operation.—As has been explained, the first operation in this case was an attempt to get results aimed in Meyer's operation on the caudate nucleus. For this purpose, 1.0 cc. of 2% procaine HCl, aqueous solution, was injected by the stereotactic technique into the head and the body of the left caudate nucleus on May 20 and 27, 1952, without any change of symptoms. On both occasions the patient became somewhat lethargic 30 minutes after injection, an effect which may have been due to diffusion of the injected narcotic to the hypothalamic level.

On June 4, injection of 1.0 cc. of the procaine, aqueous solution, was made into the left pallidum stereotactically. The effect of this was unexpectedly dramatic and conspicuous as compared with previous procedures. Both tremor and rigidity ceased immediately after injection. There was no sign of palsy or other side-effects. The level of tonicity of the affected side became almost normal, and voluntary movements improved to almost normal. After 30 minutes 1.0 cc. of procaine HCl in oil and wax was additionally injected in the same site in order to get a more lasting effect.

Results.—After operation the patient was able to walk with his arm swinging and in an upright posture. His writing and behavior were also better than before operative.

Almost complete abolition of symptoms continued for about 40 days postoperatively. After this period a tendency to reappearance of two symptoms, rigidity and tremor, was observed; but these remained far less severe than at the preoperative level, and improvement has been sustained for about 32 months, until the time of this report.

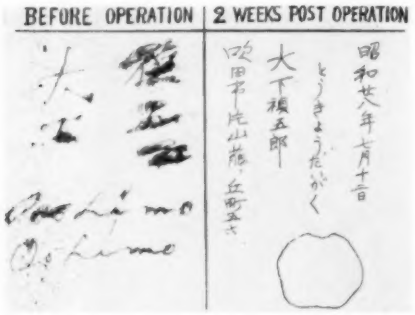


Fig. 4.—Handwriting in Case 7 before and after the operation.

Case 7 (Operation 15).—Businessman, aged 56. Diagnosis: bilateral paralysis agitans.

The onset of his disease was at the age of 50. The first sign was slight rigidity and tremor of the fingers of the right hand, which became progressively severer, spreading to the other side. On admission, rigidity and tremor were so severe that he could not write, take meals by himself, dress himself, or even turn over in bed. Tremor of the hands was typical of paralysis agitans, of pill-rolling type, and about 6 or 7 cps, with marked tremulousness of the lips, chin, and tongue. There was masking of facies, semiflexion of posture, hypersalivation, and hyperhidrosis of midgrade severity. Because of these difficulties, the patient had not been able to visit his office for more than two years, where he was the managing director of the company.

Operation.—On June 23, 1953, injection of 1 cc. of 10% procaine HCl in oil and wax was made into the left pallidum. On July 3 the same procedure was carried out on the right side. Effects were observed in both operations, not directly after operation, but in about 12 hours. Rigidity and tremor were practically absent by the following morning. This improvement was more impressive than we had anticipated. He became able to feed himself without help or to write far more easily and steadily.

Figure 4 shows the handwriting before and after operation.

In three months there was reappearance of the symptoms, but their intensity was substantially far less than before this operation. Figure 5 shows the electromyogram before and after operation.

At present, about 20 months since operation, the symptoms remain markedly improved. His everyday living has been easier, and he is visiting the office several times a month.

Case 10 (Operation 17).—Housewife, aged 45 years. Diagnosis: bilateral Parkinsonism.

Without a history of infectious disease, initial left-sided rigidity and slight tremor have progressed in the past 10 years to all extremities and to the trunk. The patient showed mask-like facies and forced laughing. Rigidity was 3+ on each side, though tremor was only 1+. On admission the patient could not hold a spoon, or even wash her hands and face. Eating a meal required about two hours. Propulsive and shuffling gait and semiflexed posture were also marked.

Operation.—In the middle of July, 1953, operations were done on the right and then to the left pallidum, with an interval of two weeks. This case was one of those with the most marked improvement, with respect both to rigidity and to tremor. This improvement showed immediately after operation and remained constant during the year she was under observation. Finger touch rate when last tested was 37 on the right and 27 on the left. Preoperatively it was 22 on the right and 13 on the left. The facies became more natural, and the patient looked younger. She was better able to perform her duties as a housewife. Vegetative hypersecretive symptoms were also reduced to a slighter degree.

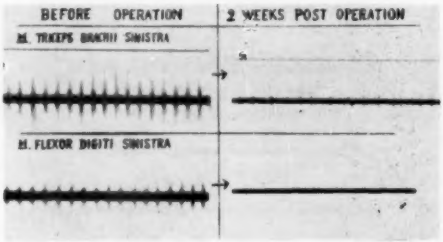
B. Rigidity Only

Case 16 (Operation 2).—A man aged 43, actor. Diagnosis: bilateral, presumably postencephalitic, Parkinsonism.

Though no history of epidemic encephalitis was confirmed, this case was assumed to be one of postencephalitic nature, because the pupils were extremely miotic and marked vegetative symptoms were observed. Since 1945, rigidity of both sides, extremities and disturbance of movement had become manifest and had progressed to the degree that he could not turn over on bed, or even pick up the bread, in spite of 18 mg. of atropine sulfate. A severe grade of mask-like facies, oculogyric crises, the typical posture of semiflexion, and the festinating and propulsive gait were observed. Tremor was so slight as to be negligible.

Operation.—Operation was done on the right pallidum on June 18, 1952, and on the left on July 20.

Fig. 5.—Electromyogram in Case 7 before and after operation.



The effect was obvious. Rigidity was reduced to almost normal, without palsy. In spite of these objective improvements, the patient did not move or work actively, but remained still, akinetic, and hypobulic. He was always lying on the bed, with a listless expression. Such a tendency could be understood as one kind of bradyphrenia.

In this case vegetative symptoms were very little improved.

Case 18 (Operation 6).—Man aged 31, a farmer. Diagnosis: bilateral Parkinsonism.

This case was thought to be of hereditary nature, as one of the patient's brothers had been suffering from tremor for six years. Since 1946, the patient had had rigidity, of increasing degree, in both lower extremities. At the time of operation this was grade 3+. He could not stamp his feet more than 20 times. The upper extremities were also so rigid that diadokokinesis and arm swinging were impossible. The pupils were normal; vegetative symptoms were slight.

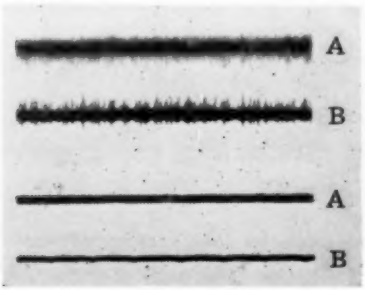
Operation.—In January, 1953, the right and then the left pallidum were operated on routinely. An effect was immediately observed with respect to rigidity, accompanied with very slight palsy of the right hypoglossal region and the upper extremities. These side-effects were transitory, and the patient had well recovered within two weeks. At present, about two years after operation,the patient is working every day as a farmer from early morning to night, without complaining of fatigue. Figure 6 shows rigidity before and after the operation.

C. Tremor Only

Case 23 (Operation 4).—A man, aged 31, a farmer. Diagnosis: right-sided tremor.

Right-handed tremor began at the age of 30, without a history of encephalitis and heredity. The symptom progressed slowly but was confined to the right side and was more marked in a vigorous

Fig. 6.—Electromyogram in Case 18 before and after the operation. Upper two tracings (at rest): (*A*) M. biceps brachii; (*B*) M. triceps brachii. Lower two tracings (after operation): (*A*) M. biceps; (*B*) M. triceps.



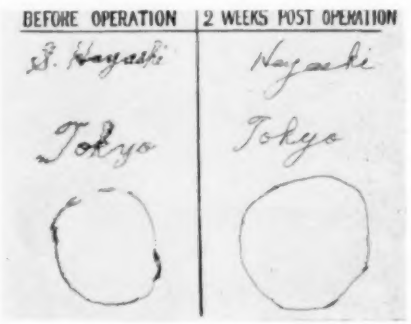


Fig. 7.—Handwriting in Case 23 before and after operation.

tremor of his right upper extremity, of 5 to 6 cps and of relatively large amplitude. Because of this tremor he could not hold a cup, handle a spoon or knife, or write with a pencil. This tremor could not be voluntarily controlled. Symptoms in the right lower extremity were relatively slight.

Operation: Dec. 6, 1952, injection of 1.0 cc. was made into the left pallidum. Immediately after the injection, the tremor ceased dramatically, followed by the improvement of movement. He was able to hold a cup, manage a spoon, and write easily. Diadokokinesis also became possible. Figure 7 shows a handwriting specimen of the patient. There was no paresis of the muscles, and their tone was almost the same as before the operation. However, within four weeks postoperatively a tendency toward reappearance of tremor was observed. Then there was gradual increase of tremor until the preoperative level was reached within the following three months.

D. Marked Vegetative Symptoms

One case which, in addition to rigidity and tremor, showed particularly marked vegetative symptoms is reported separately because of the marked effect injection had on these symptoms.

Case 26 (Operation 8).—Woman, aged 33. Diagnosis: bilateral Parkinsonism.

The patient had been born prematurely and showed psychic maldevelopment. Two years prior to the operation, tremor and rigidity of all extremities were first observed. Since then, vegetative symptoms developed and rapidly worsened. Rigidity was Grade 4+ on admission, and tremor was 2+ on each side. She could not turn over in bed or take a meal.

Operation.—On June 23, 1953, injection was made on the right side and on June 26 on the left side. With reduction of rigidity and tremor,

Data on Cases of Rigidity and Tremor in Parkinsonism

Case No.	Oper. No.	Age, Yr.	Sex	Diagnosis	Time Since Beginning, Yr.	Clinical Symptoms		Operative Date	Effect	Side-Effect	Result
						A. Rigidity and Tremor					
1	1	27	M	Right hemi-Parkinsonism	4	Right rigidity Tremor	3+ 2+	June, 1952	Immediate abolition of rigidity and tremor; voluntary movement dramatically improved	None	Symptoms reappeared to less severe degree
2	9	43	M	Right hemi-Parkinsonism	5	Right rigidity Tremor	2+ 2+	Feb., 1953	As above	None	As above
3	11	48	M	Left hemi-Parkinsonism (post-traumatic)	25	Left rigidity Tremor	3+ 1+	March, 1953	As above	None	As above
4	14	25	M	Left hemi-Parkinsonism	1	Left rigidity Tremor	3+ 1+	June, 1953	As above	Slight transient palsy of R. arm for 2 wk.	As above
5	18	55	M	Right hemi-Parkinsonism (paralysis agitans)	4	Right rigidity Tremor	2+ 1+	Aug., 1953	As above	None	As above
6	26	40	M	Right hemi-Parkinsonism	1	Right rigidity Tremor	1+ 2+	Oct., 1953	As above	None	As above
7	15	56	M	Bilateral paralysis agitans	6	Bilateral rigidity Tremor	4+ 4+	June, 1953	Diminution of rigidity and tremor 12 hr. after operation	None	As above
8	13	44	F	Bilateral Parkinsonism	4	Bilateral rigidity Tremor	4+ 1+	March, 1953	Diminution of rigidity and tremor directly after operation	Palsy of hypoglossal region	As above
9	16	50	F	Bilateral paralysis agitans	12	Rigidity Tremor	3+ 2+	June, 1953	As above	None	As above
10	17	45	F	Bilateral Parkinsonism	10	Rigidity Tremor	3+ 1+	July, 1953	As above	None	As above
11	19	46	M	Bilateral paralysis agitans	8	Rigidity Tremor (L>R)	2++ 1++	Sept., 1953	As above	None	As above
12	20	53	F	Bilateral paralysis agitans	8	Rigidity Tremor	3+ 1+	July, 1953	As above	After right-side operation, immediate palsy, followed by coma, vomiting, and high fever for about 5 days; death 7 days postoperatively	
13	23	66	F	Bilateral paralysis agitans	12	Rigidity Tremor (R<L)	4+ 3+	Oct., 1953	As above	None	As above
14	24	56	F	Bilateral paralysis agitans	8	Rigidity L R Tremor L R	3+ 2+ 2+ 1+	Oct., 1953	As above	None	As above
						B. Rigidity Only					
15	5	34	M	Left Parkinsonism	1.5	Rigidity Tremor	3+ —	Dec., 1952	Reduction of rigidity directly after operation	None	Effect sustained
16	12	43	M	Postenceph. Parkinsonism	9	Rigidity Tremor	3+ —	June, 1952	As above, but patient remained hypokinetic	Slight palsy of L. arm for 1 wk.	As above
17	3	34	F	Bilateral Parkinsonism	3	Rigidity Tremor	3+ —	May, 1952	As above	None	As above
18	6	31	M	Bilateral Parkinsonism	6	Rigidity Tremor	3+ —	Jan., 1953	Reduction of rigidity	None	Patient almost normal
19	10	41	M	Bilateral postenceph. Parkinsonism	3	Rigidity Tremor	3+ —	Feb., 1953	As above	Palsy of L. lower extremity for 3 wk.	Effect sustained
20	12	55	M	Paralysis agitans	4	Rigidity Tremor	4+ —	March, 1953	As above	Right-sided capsular palsy for 1 mo.	As above
21	21	54	M	Postenceph. Parkinsonism	13	Rigidity Tremor	3+ —	Sept., 1953	As above	None	As above, but patient hypokinetic
22	25	41	M	Bilateral Parkinsonism	11	Rigidity Tremor	4+ —	Nov., 1953	As above	None	As above
						C. Tremor Only					
23	4	31	M	Right hemitremor	1	Tremor R. hand	4+	Dec., 1952	Dramatical abolition of tremor immediately after operation	None	Tremor reappeared and became manifest within 1 mo.
24	7	28	M	Right hemitremor	8	Tremor R. hand	4+	Jan., 1953	As above	None	As above
25	22	35	M	Bilateral tremor	6	Tremor in all extremities	4+	Sept., 1953	Tremor unchanged	None	As above

marked hyperhidrosis and hypersalivation decreased to almost normal level, and seborrhea of the face became less impressive. It was interesting that the preoperative necessity of changing nightgowns several times during the night because of soaking perspiration, a very troublesome duty for the nurses, was no longer present after the operation.

These effects on the vegetative symptoms have been sustained for more than 20 months.

Rigidity and tremor were also improved bilaterally, postoperative rigidity being 2+. Tremor has also become less disturbing.

COMMENT

Twenty-six cases were observed after surgery, for periods of 18 to 32 months. A summary of our experience with the cases in the various symptomatic groups, i. e., those with tremor alone or rigidity alone or both, follows:

1. In every case with muscle rigidity except one blocking of the globus pallidus immediately reduced the rigidity to an approximately normal level. In Case 15 abolition of rigidity was not observed until the morning after surgery. With improvement of rigidity, rapid and fine voluntary movements, finger touch, diadokokinesis, etc., became easier and more natural. Associated movements and speech were also improved, in varying degrees. Facial rigidity became less, and the patient's appearance was calmer and more natural. In the most dramatic cases the preoperative bilateral Parkinsonism resembled hemi-Parkinsonism after the unilateral pallidotomy. In our cases rigidity fell only to the normal tonic level, and not to a hypotonic level, unless capsular palsy was produced. In the case that capsular palsy was produced muscle became hypotonic, with disturbance of voluntary movements. This fact suggests that the globus pallidus should not be considered the center, or at least the only center, governing muscle tone in the simple meaning of "center," i. e., a locus the stimulation of which results in hyperfunction and the destruction of which results in the loss of function.

The postoperative course of improved rigidity is schematically shown in Figure 8. In most cases reduced muscle rigidity showed some tendency to reappear about 3 to 10 weeks after operation, though slowly and in varying degrees. Generally, after three months the recurrent rigidity reached a level far lower than the preoperative one. The

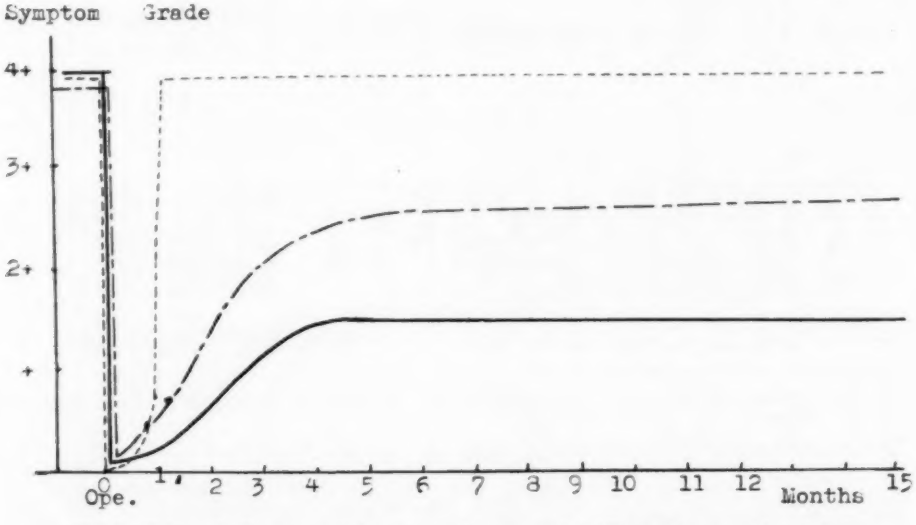


Fig. 8.—Schematically represented postoperative course of rigidity and tremor. Line of dashes indicates course in case of tremor only; solid line, course in case of rigidity only, and line of dashes short and long dashes, course in case of both rigidity and tremor.

degree of rigidity after pallidotomy paralleled the severity of preoperative rigidity.

2. In each case with tremor the operation initially diminished or abolished this symptom. Except for Case 15, the effect was immediate. In the one case (15) the effect was not apparent until the morning after surgery. However, there was greater tendency to relapse from the improvement of tremor than from rigidity. Cases with tremor but not rigidity, such as Cases 23 and 24, showed complete recovery after operation, but tremor soon began to reappear, reaching preoperative levels in several weeks. In cases with rigidity and tremor, the tremor showed sustained improvement, corresponding to the improvement in rigidity. Apparently, this procedure produces its effect on tremor indirectly by affecting muscle tone, but not directly. Therefore our operation can be expected to improve tremor only when there is coexistent rigidity. The operation is not indicated in cases with tremor alone.

3. In nine patients with vegetative dysfunction, such as hyperhidrosis, hypersalivation, and seborrhea of the face, the operation was effective, in varying degrees. Hypersecretion decreased in one case almost to the normal state. In some cases the change was found on the side opposite the operation and in others on both sides, after unilateral operation. We cannot explain this variation in laterality.

4. The most significant side-effect of this operation is supranuclear palsy, due to capsular invasion. With exact stereotactic technique, puncture of the internal capsule can usually be avoided. It is possible to damage the internal capsule with the injected mass, because its diameter is about 0.6-1.0 cm. However, palsy is usually transient. In lesions involving the tongue fibers recovery may be slow and troublesome.

Other side-effects, such as headache, nausea and vomiting, fever, or disturbance of consciousness, are not frequent in this operation.

The mortality with this operation was 1 in 26 cases. This death was the result of intracerebral bleeding. We feel that, with more experience, the likelihood of hemorrhage can be reduced.

Another possible complication is puncture of the lateral ventricles, and instilling even a drop of procaine oil into the ventricular system may mean a serious one. This is a theoretical consideration, and no such accident occurred in our series.

5. This operation seems to have the same effect on postencephalitic Parkinsonism as on paralysis agitans. The results differed only according to grade and combination of the preoperative symptoms. Hence, the prognosis seems to be dependent on symptoms, and not on etiology. With the data now available, the mechanism of involuntary movement cannot be explained with certainty. The theory of the suppressor system has gained enough acceptance that neurosurgical procedures designed to alleviate the symptoms of Parkinsonism have been based on it. However, our results tend to refute, rather than support, this theory. Destruction of the globus pallidus, which is considered an important part of the suppressor system, has resulted in only transitory lessening of tremor and more or less permanent reduction in muscle rigidity. We suggest that this nucleus is concerned more with muscle tone than with involuntary movement.

Tremor can be influenced only with improvement of rigidity. These two symptoms are related, but rigidity seems to be more important. Improvement in rigidity makes tremor more controllable and less manifest. Electrical stimulation of the globus pallidus at operation suggests its importance in producing muscle rigidity. This was reported at the 51st Conference of Neuropsychiatry of Japan at Nagoya City in April, 1954. Stimulation produces primarily increased rigidity and slight increase in tremor. Briefly described, the threshold voltage of the electrical stimulation of the globus pallidus, using square waves of 3 msec. and 40 cycles, is in most cases a little higher, i. e., 10-12 volts, than that of the pyramidal tract (4-6 volts). The effect of stimulation of this nucleus is usually observed in increase of tonicity of muscles, though the internal capsule stimula-

tion results in contraction of muscles corresponding to the stimulation. Tremor does not increase by stimulation of the globus pallidus except when coexistent rigidity is increased.

There is much evidence that degeneration of the substantia nigra is the primary pathological alteration in Parkinsonism. We infer from our results that degeneration of the substantia nigra may result in releasing control over the globus pallidus and in producing muscle hypertonus. The globus pallidus in such a condition appears to play an accelerating role in production of muscle rigidity, and its destruction might be thought to cause lowered rigidity. However, the reverse appears to be true, for in carbon monoxide poisoning degeneration of the globus pallidus results in a hypertonic, rigid state. These facts appear contradictory. We think that the globus pallidus and the substantia nigra constitute one system or unit regulating muscle tone, destruction of one part of which may cause hypertonus, and that almost total destruction of both nuclei results in extinction of this hypertonic state. At any rate, the globus pallidus can be considered rightly to be the point to be attacked by the neurosurgical procedure for relief of the Parkinsonian state.

SUMMARY

The authors performed stereotactically guided injections of the procaine oil and wax mixture into the globus pallidus for the treatment of Parkinsonism in 26 cases. The principal symptoms were dramatically influenced and relieved by this method, without any undesirable side-effect in most cases. Improvement was observed immediately after operation.

Reduction of rigidity was sustained, but tremor showed a tendency to reappear within several weeks. Improvement in tremor depends on improvement of the coexistent rigidity. Indication for this operation is mainly rigidity and less tremor.

Operative mortality was 1 case in 26, caused by intracerebral bleeding during insertion of the needle. The only notable side-effect was supranuclear palsy. This complication can be avoided by exact stereotactic technique.

Vegetative symptoms were improved by this operation in several cases.

The neurophysiological implications of the results concerning the role of the globus pallidus in genesis of rigidity and tremor are discussed. The theory of the suppressor system is criticized in the light of our findings.

BIBLIOGRAPHY

Beheim-Schwarzbach, D.: Über Zelleib-veränderungen im Nucleus coeruleus bei Parkinson-Symptomen, J. Nerv. & Ment. Dis. **116**:619, 1952.

Bucy, J. C.: Cortical Extirpation in the Treatment of Involuntary Movement, A. Res. Nerv. & Ment. Dis., Proc. (1940) **21**:551, 1942.

Neural Mechanisms of Athetosis and Tremor, J. Neuropath. & Exper. Neurol. **1**:224, 1942.

——and Buchanan, D. N.: Athetosis, Brain **55**:479, 1932.

——and Case, T. J.: Athetosis: II. Surgical Treatment of Unilateral Athetosis, Arch. Neurol. & Psychiat. **37**:983, 1937.

Tremor: Physiologic Mechanism and Abolition by Surgical Means, Arch. Neurol. & Psychiat. **41**:721, 1939.

Effron, A. S., and Denker, P. G.: A Clinical Evaluation of Certain Antihistaminic and Antispasmodic Drugs in Parkinson's Disease, J. A. M. A. **144**:5, 1950.

Fenyes, I.: Alzheimersche Fibrillenveränderung im Hirnstamm einer 28 jährigen Postencephalitikerin, Arch. Psychiat. **96**:700, 1932.

Foerster, O.: Zur Analyse und Pathophysiologie der striären Bewegungsstörungen, Ztschr. ges. Neurol. u. Psychiat. **73**:1, 1921.

Gamper, E.: Paralysis agitans, in Bumke, O., and Foerster, O., Editors: Handbuch der Neurologie, Berlin, Springer-Verlag, 1936, Vol. 16.

Godlowski, W. J.: Die Ganglienzelleinschlüsse in der Substantia nigra, Arb. Neurol. Inst. Wien. **33**:14, 1931.

Goldstein, K.: Über anatomischen Veränderungen bei postencephalitischen Parkinsonismus, Ztschr. ges. Neurol. u. Psychiat. **76**:627, 1922.

Hallervorden, J.: Zur Pathogenese der postencephalitischen Parkinsonismus, Klin. Wchnschr. **12**:692, 1933.

Anatomische Untersuchungen zur Pathogenese der postencephalitischen Parkinsonismus, Zentrabl. Neurol. **74**:427, 1935; Deutsche Ztschr. Nervenh. **136**:68, 1935.

Hassler, R.; Zur normal Anatomie der Substantia nigra, J. Psychol. u. Neurol. **48**:1, 1937.

Zur Pathologie der Paralysis agitans und des postenzephalitischen Parkinsonismus, J. Psychol. u. Neurol. **48**:387, 1938.

Zur pathogischen Anatomie des senilen und des parkinsonischen Tremor, J. Psychol. u. Neurol. **49**:193, 1939.

Holzer, W.: Über die anatomische Grundlage der Paralysis agitans, Arch. Psychiat. **112**:327, 1940.

Die Glianarbe im Nach- und Zwischenhirn nach Encephalitis epidemica, Ztschr. ges. Neurol. & Psychiat. **104**:503, 1926.

Hunt, J. R.: Progressive Atrophy of the Globus Pallidus, Brain **40**:58, 1917.

Striocerebellar Tremor, Arch. Neurol. & Psychiat. **8**:664, 1922.

Jacob, A.: Die extrapyramidale Erkrankungen, Berlin, Springer-Verlag, 1923.

Jelgersma, G.: Neue anatomische Befunde bei Paralysis agitans und bei chronische Chorea, Neurol. Centralbl. **27**:995, 1908.

Klaue, R.: Zur vorstehende Arbeit von W. Holzer, Arch. Psychiat. **112**:341, 1940.

Parkinsonische Krankheit und postencephalitischen Parkinsonismus, Arch. Psychiat. **112**:251, 1940.

Klemme, R. M.: The Surgical Treatment of Parkinson's Disease, Mod. Med. **12**:453, 1945.

Oculogyric Crisis, Am. J. Ophth. **24**:1000, 1941.

——and Minckler, J.: Role of the Premotor Cortex in Human Motor Activity, Proc. Soc. Exper. Biol. & Med. **53**:1264, 1943.

Lewy, F. H.: Die Lehre von Tonus und Bewegung, Berlin, Springer-Verlag, 1923.

Lotmar, F.: Hypokinetische und hypertonische Syndrom, in Bumke, O., and Foerster, O., Editors: Handbuch der Neurologie, Berlin and Wien, Springer-Verlag, 1923, Vol. 5, p. 428.

Lucksch, F., and Spatz, H.: Die Veränderungen im Zentralnervensystem bei Parkinsonismus in den Spätstadien der Encephalitis epidemica, München. med. Wchnschr. **70**:1245, 1923.

Meyers, R.: Surgical Procedure for Postencephalitic Tremor, with Notes on the Physiology of Premotor Fibers, Arch. Neurol. & Psychiat. **44**:455, 1940.

Surgical Experiments in the Therapy of Certain Extrapyramidal Diseases: A Current Evaluation, Acta psychiat. et neurol., Supp. 67, 1951.

Narabayashi, H.: Stereoencephalotom: II., Psychiat. et neurol. japon. **54**:669, 1953.

——and Okuma, T.: Procaine Oil Blocking of the Globus Pallidus for Treatment of Double Athetoses, Psychiat. et. neurol. japon. **54**:672, 1952.

Procaine-Oil Blocking of the Globus Pallidus for the Treatment of Rigidity and Tremor of Parkinsonism: Preliminary Report, Proc. Jap. Acad. **29**:134, 1953.

Stereoencephalotomy: Review of Its Technic and Theory (Review and Technic), Brain and Nerve **5**:348, 1953.

Some Contemplations on the Role of the Globus Pallidus in Parkinsonism, Brain & Nerve **6**:157, 1954.

Oliver, L. C.: Surgery in Parkinson's Disease, Lancet **1**:847, 1950.

Papez, J. W.; Hertzman, J., and Rundles, R. W.: Athetosis and Pallidal Deficiency, Arch. Neurol. & Psychiat. **40**:789, 1938.

Patrick, H. T., and Lewy, D. M.: Parkinson's Disease, Arch. Neurol. & Psychiat. **7**:711, 1922.

Putnam, T. J.: Treatment of Unilateral Paralysis Agitans by Section of the Lateral Pyramidal Tract, Arch. Neurol. & Psychiat. **44**:950, 1940.

Results of Treatment of Athetosis by Section of Extrapyramidal Tracts in the Spinal Cord, Arch. Neurol. & Phychiat. **39**:258, 1938.

Sachs, E.: Subpial Resection of the Cortex in the Treatment of the Jacksonian Epilepsy with Observation on Area 4 and 6, Brain **58**:492, 1935.

Sasaki, R.: On the Aminohydrocarbostyril and Aminophenyl Derivatives, Nippon Seikagakukai Kaiho **5**:127, 135, 1930.

Schlesinger, E. B.; Drew, A. L., and Wood, B.: Clinical Studies in the Use of Myanesin, Am. J. Med. **4**:365, 1948.

Sloan, N., and Jasper, H.: Identity of Spreading Depression and Suppression, Electroencephalog. & Clin. Neurophysiol. **2**:59, 1950.

Spatz, H.: Encephalitis, in Bumke, O., and Foerster, O., Editors, Handbuch der Neurologie, Berlin, Springer-Verlag, 1936, Vol. 11, p. 254.

Spiegel, E. A., and Wycis, H. T.: Pallidothalamotomy in Chorea, Arch. Neurol. & Pspchiat. **64**:295, 1950.

Anatomy in Paralysis agitans, Confinia neurol. **12**:245, 1952.

Principles and Applications of Stereoencephalotomy, J. Internat. Coll. Surgeons **14**:394, 1950.

Role of Pallidum in Genesis of Some Choreic Movements, Neurology **3**:261, 1953.

Stereoencephalotomy, New York, Grune & Stratton, Inc., 1952.

Thalamotomy and Pallidotomy for Treatment of Choreic Movements, Acta neurochir. **2**:417, 1952.

Stern, F.: Epidemische Encephalitis (Economosche Krankheit), in Bumke, O., and Foerster, O., Editors: Handbuch der Neurologie, Berlin, Springer-Verlag, 1936, Vol. 13, p. 410.

Straube, G.: Zur Frage der traumatischen Entstehung der Paralysis, Deutsche Ztschr. Nervenh. **134**:31, 1934.

Takebayashi, H.: T-tomy: New Technique in Extrapyramidal Surgery, Med. J. Osaka Univ., Vol. 2, No. 4, p. 1, 1951.

Talairach, J.; Paillas, J. E., and David, M.: Dyskinésie de type hémiballique traitée par cortectomie frontale limitée, puis par coagulation de l'anse lenticulaire et de la portion interne du globus pallidus: Amélioration importante depuis un an, Rev. neurol. **83**:440, 1950.

Uchimura, Y., and Narabayashi, H.: Stereoencephalotom: I., Psychiat. et neurol. japon. **52**:265, 1951.

Vogt, C., and Vogt, O.: Zur Lehre der Erkrankungen des striären Systems, J. Psychol. u. Neurol. **25**:627, 1920.

Walshe, F. M. R.: Nature of the Muscular Rigidity of Paralysis Agitans and on Its Relationship to Tremor, Brain **47**:159, 1924.

Bailey, O. T.; Small, W. T., and Ingraham, F. D.: Procaine Block of Frontal Lobe White Fibers as a Means of Predicting the Effect of Prefrontal Lobotomy: I. Experimental Studies, J. Neurosurg. **9**:21, 1952; II. Clinical Evaluation, ibid. **9**:30, 1952.

Wilson, S. A. K.: Disorders of Motility and of Muscle Tone, Lancet **2**:215, 1925.

Die Pathogenese der unwillkürlichen Bewegungen mit besonderer Berücksichtigung der Pathologie und Pathogenese der Chorea, Deutsche Ztschr. Nervenh. **108**:4, 1929.

Some Effects of Bufotenine and Lysergic Acid Diethylamide on the Monkey

EDWARD V. EVARTS, M.D., Bethesda, Md.

INTRODUCTION

Bufotenine (5-hydroxy-3-[2-dimethylaminoethyl]-indole) is the N-dimethyl derivative of the vasoconstrictor substance serotonin (5-hydroxytryptamine). It was first synthesized by Wieland in 1934. Raymond-Hamet found that intravenous injection of bufotenine caused transient elevation of blood pressure and apnea, followed by tachypnea, in anesthetized dogs.* To date, however, there is little published material concerning the effects of bufotenine on unanesthetized animals. Our interest in such effects was based on the fact that bufotenine was recently isolated from the bean of Piptadenia peregrina,[5] a bean long known to be the source of cohoba, a narcotic snuff. This snuff has been used by inhabitants of the West Indies to induce hallucinations and mystical states,[6] states which seem similar to those produced by mescaline, harmine, and lysergic acid diethylamide. It was felt, in view of the reported psychological effects of bufotenine-containing snuff, that it would be worth while to investigate the effects of bufotenine on unanesthetized monkeys.

The effects of lysergic acid diethylamide (LSD-25) on unanesthetized monkeys were studied for similar reasons. As is well known, LSD-25 in minute doses produces marked alterations of mood and perception in man. Extensive clinical investigations of the effects of LSD-25 have been reported.† As little as 0.001 mg/kg. of LSD-25 has produced psychological alterations that have been compared to schizophrenia. The present study was carried out to gain knowledge of the effects of LSD-25 in doses higher than may safely be administered to man.

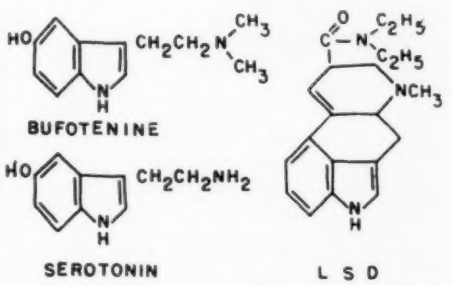


Fig. 1.—Structures of lysergic acid diethylamide (LSD), bufotenine, and serotonin.

The structures of bufotenine, LSD-25, and serotonin are shown in Figure 1.

MATERIALS AND METHODS

Eight immature monkeys (Macaca mulatta), weighing from 3 to 4.5 kg., were used as subjects. Bufotenine,‡ as the free base, was dissolved in creatinine sulfate solution, 1 part of bufotenine to 1.6 parts of creatinine sulfate by weight. Doses of bufotenine refer to the free base. Aqueous solutions of LSD-25 were freshly prepared from crystalline material. Solutions were prepared immediately before injection and were administered via the saphenous vein.

The accompanying Table lists observations which were carried out. In addition, attempts were made

Received for publication Aug. 2, 1955.

National Institute of Mental Health, National Institutes of Health, U. S. Public Health Service, Department of Health, Education, and Welfare.

* References 2 to 4.

† References 7 to 9.

‡ The bufotenine used in these experiments was extracted from the bean of Piptadenia peregrina by Dr. V. Stromberg, of the National Heart Institute, and was supplied to the author by Dr. Evan Horning, of the National Heart Institute.

Effects of Lysergic Acid Diethylamide (LSD-25) and Bufotenine on the Monkey *

Observation	LSD-25 1.0 Mg./Kg. Effect	LSD-25 1.0 Mg./Kg. Duration, Min.	Bufotenine 5.0 Mg./Kg. Effect	Bufotenine 5.0 Mg./Kg. Duration, Min.
Muscle power	Grossly normal	.....	Grossly normal	.....
Deep tendon reflexes	Grossly normal	.....	Hyperactive	15
Vestibular eye movements	Grossly normal	.....	Grossly normal	.....
Reaction to auditory stimuli	Grossly normal	.....	Grossly normal	.....
Pupillary light reflex	Present	.....	Present	.....
Locomotion	Ataxic	55 (20-85)	Ataxic	50 (20-90)
Reaction to painful stimuli	Absent	65 (30-95)	Absent	67 (35-110)
Reaction to visual stimuli	Absent	77 (35-103)	Absent	69 (45-110)
Reaction to handling	Marked tameness	110 (85-130)	Marked tameness	105 (70-120)

* This Table lists certain of the effects of LSD-25 and bufotenine and gives the mean and range of duration of these effects following injection.

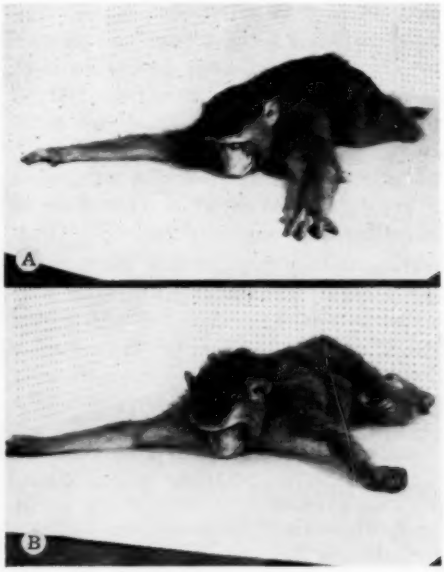
to estimate changes in general behavior of the monkey when handled by the examiner. Observations were carried out with the subject either in his cage or free in an examining room in which he could run about unimpeded. Subjects were deprived of food for 24 hours preceding experiments. Monkeys were used repeatedly, but never more than once a week.

RESULTS

The Table lists the effects of 1.0 mg/kg. of LSD-25 and 5.0 mg/kg. of bufotenine.§ The similarity of effect of the two substances is apparent. The drug effects indicated in the Table were generally maximal within one minute following injection.

During approximately the first 20 minutes following drug administration, subjects did not walk or climb. During this period they maintained a constant prone position (Fig. 2), which they vigorously maintained in spite of attempts to place them in any other position. In their attempts to regain the prone position, when displaced, they demonstrated good muscular power. Another demonstration of preserved muscular power is indicated in Figure 3. This Figure shows monkeys, within five minutes following injections of LSD-25 and bufotenine, holding onto the experimenter's finger; subjects were able to maintain this hold for long periods, despite attempts by the experimenter to shake them loose. The prone position was maintained for approximately 20 minutes, after which monkeys assumed a sitting posture and began to make attempts to move about. Their movements generally consisted of ataxic circling. Within an average of 55 minutes following injection, ataxia had become slight to absent. There remained, however, lack of response to visual stimuli and absence of reaction to noxious stimuli. After reaction to painful stimuli returned, usually at about 65 minutes following drug injection, only blindness and unu-

Fig. 2.—Effects of LSD-25 and bufotenine on position. This Figure shows the position assumed immediately following injection of LSD-25 (*A*) and bufotenine (*B*).



§ Though the effects of a wide range of doses were studied, only the effects of the highest doses used are presented. The reason for this is the fact that the observations reported were most clearly present at these high doses and may be most simply and concisely described for these dosage levels.

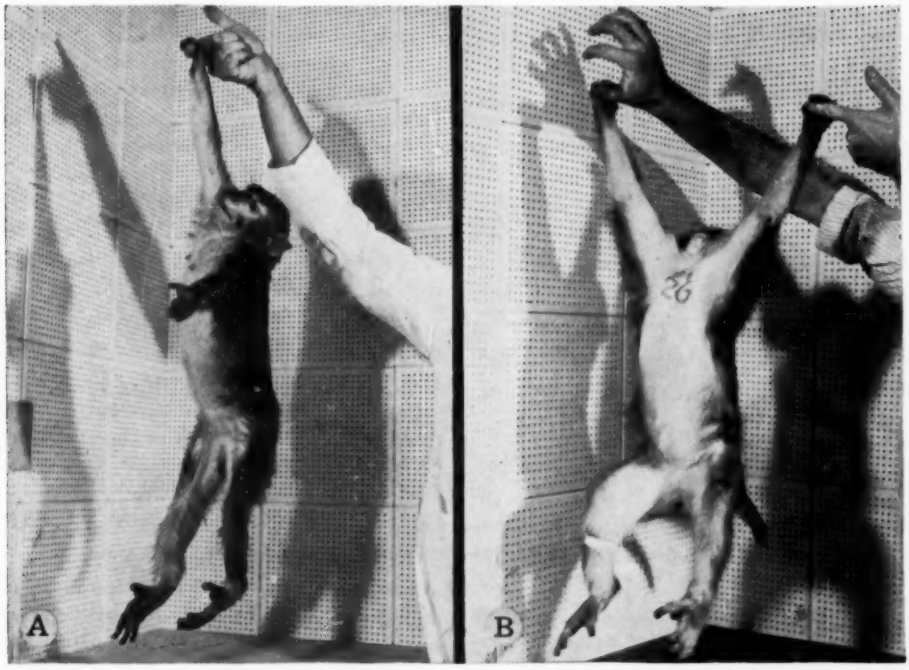
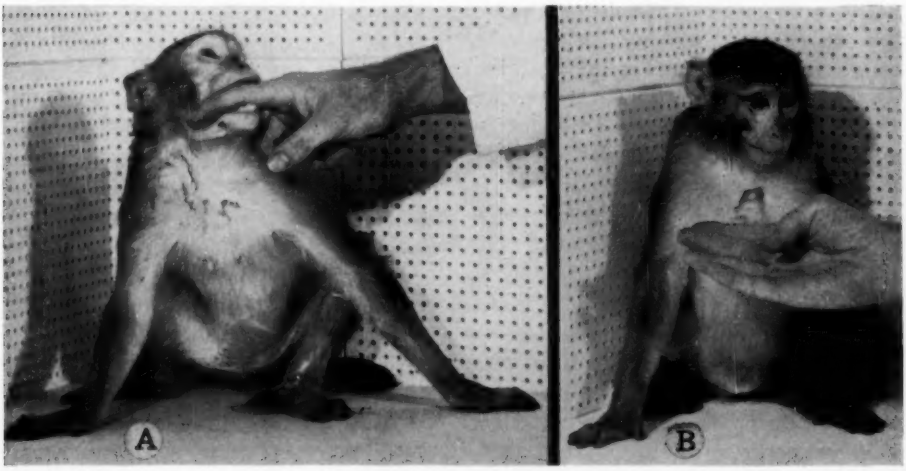


Fig. 3.—Effects of LSD-25 and bufotenine on motor power. This Figure demonstrates the ability of subjects to support their own weight immediately after LSD-25 (*A*) and bufotenine (*B*).

Fig. 4.—Taming effects of LSD-25 and bufotenine. This Figure shows striking tameness of subjects one hour following LSD-25 (*A*) and bufotenine (*B*).



sual tameness remained of the original symptoms. At this stage the monkey would run about the examining room without ataxia, but would bump headlong into any objects interposed in its path. No reactions to moving objects or lights could be discovered. After visual reactions had returned, an unusual degree of tameness persisted. It was possible to place one's finger in the monkey's mouth with impunity (Fig. 4). Within one and a half to two hours of drug injection, the monkeys had usually become grossly normal, the only residual effect being a decreased tendency to climb and jump about the cage.

COMMENT

The most prominent feature of the effects of LSD-25 and bufotenine in monkeys is the occurrence of a marked impairment of function in certain sense modalities in the absence of a clear defect of muscular power. The predominance of sensory disorder is well demonstrated (during the period between 55 and 75 minutes following injection of LSD-25) by the presence of impaired visual responsiveness in an animal that can, at the same time, run about the room with agility. The disturbance of locomotion and the unusual posture assumed by subjects during the early stage of drug effect might also be looked upon as sensory in origin. Lassek [10] has shown that posterior rhizotomy leads to "inactivation of motor function." Goody [11] has pointed out that purposive movement is dependent upon a continuous input of proprioceptive impulses. One may take the data of these authors as supporting the notion that the disorder of movement seen in monkeys following LSD-25 and bufotenine might well be related to a disorder of proprioceptive sensation, rather than to a primary disorder of the efferent motor system.

In addition to the dissociation of defects within the motor and sensory fields, there was dissociation of defects within various sense modalities. Auditory and vestibular reactions were not clearly disturbed at any time. Moreover, function returned at differential rates in those modalities that were affected. Proprioceptive sensation, disturbed initially, returned gradually and was not grossly deficient at a point when responses to visual and noxious stimuli were still absent. Reactions to pain generally returned before visual reactions, though in some animals this was not the case. Tameness, apparent through the period of gross sensory disorder, remained even after responsiveness to gross visual and tactile stimuli had returned.

The nature of this drug-induced syndrome suggests the speculation that these drugs may alter transmission of sensory impulses. Experiments at this Institute have shown that this is the case. In studies of the effects of LSD and bufotenine on neural transmission in the visual system of the cat,[12] we have found that LSD-25 and bufotenine block transmission in the lateral geniculate nucleus.

The experiments reported here may cast some light on the pharmacological mechanism of the action of LSD-25 and bufotenine, which, however, must remain a matter of speculation. Page,[13] in a recent review devoted to 5-hydroxytryptamine (serotonin), suggested that LSD-25 might act by antagonizing some presently unknown function of serotonin in the central nervous system. He based this speculation on Gaddum's [14] discovery that LSD-25 is a highly potent serotonin antagonist, inhibiting serotonin action on rat uterus in concentrations as low as 10^{-6}. Wooley [15] has put forward the idea that the central effects of LSD-25 are due to serotonin antagonism, basing this notion on his finding that harmine, as well as LSD-25, is a serotonin antagonist. Harmine has long been known to produce LSD-25-like effects.[16] Our observation that bufotenine has effects in monkeys which are similar to those of LSD-25, both behaviorally and electrophysiologically, adds weight to the idea that LSD-25 and bufotenine may owe their neuropsychological effects to the fact that they are serotonin analogues. Such an idea must be clearly labeled as speculation at the present time, however, since no direct evidence has

yet been developed to prove the point. Studies of the function of serotonin in the central nervous system, it may be hoped, will elucidate this matter.

SUMMARY

Lysergic acid diethylamide (LSD-25) and bufotenine, in doses of 1.0 and 5.0 mg/kg. injected intravenously, produce a syndrome characterized by gross sensory disorder in the absence of a clear defect in muscle power, and by a marked degree of tameness.

Laboratory of Clinical Science.

REFERENCES

1. Wieland, H.; Konz, W., and Mittasch, H.: Die Konstitution von Bufotenin und Bufotenidin, Ann. Chem. **513**:1, 1934.

2. Raymond-Hamet: Sur l'Action vasculaire locale de la bufoténine, Compt. rend. Soc. biol. **135**: 1414, 1941.

3. Raymond-Hamet: Sur les Effets vaso-constricteurs renaux de la bufotaline, Compt. rend. Soc. biol. **137**:178, 1943.

4. Raymond-Hamet: Sur la Constance et la résistance au temps du venin desséché de *Bufo Bufo Bufo*, Compt. rend. Soc. biol. **147**:301, 1953.

5. Stromberg, V. L.: The Isolation of Bufotenine from Piptadenia Peregrina, J. Am. Chem. Soc. **76**:1707, 1954.

6. Safford, W. E.: Identity of Cohoba, the Narcotic Snuff of Ancient Haiti, J. Washington Acad. Sc. **6**:547, 1916.

7. Stoll, W.: Psychische Wirkung eines Mutterkornstoffes in ungewöhnlich schwacher Dosierung, Schweiz. med. Wchnschr. **79**:110, 1949.

8. Savage, C.: Lysergic Acid Diethylamide (LSD-25): A Clinical-Psychological Study, Am. J. Psychiat. **108**:896, 1952.

9. Hoch, P. H.; Cattell, J. P., and Pennes, H. H.: Effects of Mescaline and Lysergic Acid Diethylamide (d-LSD-25), Am. J. Psychiat. **108**:579, 1952.

10. Lassek, A. M.: Inactivation of Voluntary Motor Function Following Rhizotomy, J. Neuropath. & Exper. Neurol. **12**:83, 1953.

11. Goody, W.: Sensation and Volition, Brain **72**:312, 1950.

12. Evarts, E. V.; Landau, W.; Freygang, W., Jr., and Marshall, W. H.: Some Effects of Lysergic Acid Diethylamide and Bufotenine on Electrical Activity in the Cat's Visual System, Am. J. Physiol. **182**:594, 1955.

13. Page, I. H.: Serotonin (5-Hydroxytryptamine), Physiol. Rev. **34**:563, 1954.

14. Gaddum, J. H., and Hameed, K. A.: Drugs Which Antagonize 5-Hydroxytryptamine, Brit. J. Pharmacol. **9**:240, 1954.

15. Wooley, D. W., and Shaw, E.: A Biochemical and Pharmacological Suggestion About Certain Mental Disorders, Science **119**:587, 1954.

16. Iberico, C. C.: Ayahuasca, Bol. mus. Hist. Nat. (Lima, Peru) **5**:313, 1941.

The Accumulation of S^{35}-Chlorpromazine in Brain

ARTHUR W. WASE, Ph.D.
JENS CHRISTENSEN, M.D.
and
EDWARD POLLEY, Ph.D., Philadelphia

In view of reports indicating damage to the liver following the use of chlorpromazine * and our earlier observations [3] indicating S^{35}-chlorpromazine to be rapidly accumulated in brain tissue, it was decided to study the pattern of accumulation of this new important therapeutic agent upon repeated administration.

EXPERIMENTAL

Twenty-four adult male rats (150-200 gm.) were divided into four groups and given daily intraperitoneal injections of S^{35}-chlorpromazine (50 mg/kg.). One group was killed each day, so that samples of animals having one, two, three, and four doses of chlorpromazine were obtained. The animals were killed by exsanguination, followed by perfusion with saline. The brains were carefully dissected into the important anatomical sections indicated below. The tissues, liver and brain, were separated into protein and lipid fractions by precipitating 1:10 aqueous homogenates (plasma was diluted with water) with 10 volumes of acetone-alcohol-ether mixture (1:1:1). The protein precipitate was separated by centrifugation and extracted five to six times with the hot acetone mixture. The lipid extracts were combined, evaporated to dryness on a steam bath, and prepared for radioassay in thin films of a density adjusted to 0.1 mg/sq. cm. Protein was assayed similarly after solution in 3 N KOH. Radioassay was performed with the aid of a gas-flow detector, and counting was continued to give a 1%-2% statistical reliability. The results are indicated in Tables 1 to 3.

Received for publication Aug. 8, 1955.

Divisions of Biochemistry, Pharmacology, and Anatomy, Hahnemann Medical College and Hospital of Philadelphia.

* References 1 and 2.

TABLE 1.—*Accumulation of S^{35} from S^{35}-Chlorpromazine After Repeated Administration*

Daily Doses	Tissue	Cpm/Gm. Lipid	Cpm/Gm. Protein
1	Cortex	80	Trace
2	Cortex	1,100	None
3	Cortex	34,000	None
4	Cortex	31,200	None
1	Pons, medulla, and mesencephalon	14,800	None
2	Pons, medulla, and mesencephalon	21,100	None
3	Pons, medulla, and mesencephalon	31,200	None
4	Pons, medulla, and mesencephalon	31,900	None
1	Hypothalamus	21,200	None
2	Hypothalamus	51,100	None
3	Hypothalamus	62,500	None
4	Hypothalamus	100,000	None
1	Thalamus	31,000	None
2	Thalamus	32,400	Trace
3	Thalamus	14,100	None
4	Thalamus	16,500	None
1	Cerebellum	9,100	None
2	Cerebellum	28,000	None
3	Cerebellum	22,100	None
4	Cerebellum	19,200	None

TABLE 2.—*Distribution of Activity from S^{35}-Chlorpromazine in the Liver of the Rat*

No. Daily Doses	Cpm/Gm. Lipid	Cpm/Gm. Protein	Ratio Protein Activity/ Fat Activity
1.	16,600	769	0.048
2.	28,700	1,293	0.045
3.	23,000	1,330	0.058
4.	25,300	2,073	0.082

TABLE 3.—*Activity of Blood Plasma of Rats Receiving S^{35}-Chlorpromazine*

No. Doses	Cpm/Gm. Lipid
1.	3,670
2.	7,000
3.	7,670
4.	7,500

The second experiment employed six groups of six adult male rats. Two of the groups were given nonradioactive chlorpromazine 25 mg/kg., and two groups, 50 mg/kg., while the remaining two groups served as controls. Thirty minutes later all groups were given 100μc of carrier-free P^{32} (as $PO_4^{\equiv}$). The animals of one of each of the above treated and control groups were killed (as above) 24 and 48 hours later. The brains were removed and dissected and the phospholipids extracted by the method of Bloor. In the first run of this experiment, the extracted phospholipids were assayed, as described, above, in uniformly thin layers. In the second trial, the phospholipid phosphorus was determined and the specific activity (cpm/μM P) estimated. Results are indicated in Table 4.

TABLE 4.—*Effect of Chlorpromazine on the Phospholipid Turnover of the Rat Brain*

Dose (Mg./Kg.)	Anatomical Area	Exper. 1 Cpm/Mg. Phospholipid		Exper. 2 Cpm/μM Lipid P	
		24 Hr.	48 Hr.	24 Hr.	48 Hr.
None	Hypothalamus	142	331	291	4,940
5	Hypothalamus	170	334	405	1,955
10	Hypothalamus	197	296	522	1,751
None	Cortex	155	180	275	521
5	Cortex	146	186	263	718
10	Cortex	103	184	169	278
None	Cerebellum	232	261	477	514
5	Cerebellum	187	224	410	806
10	Cerebellum	128	307	362	416
None	Thalamus	96	130	207	204
5	Thalamus	88	106	181	310
10	Thalamus	95	149	190	209
None	Pons, medulla, and mesencephalon	116	148	210	206
5	Pons, medulla, and mesencephalon	96	160	246	311
10	Pons, medulla, and mesencephalon	107	170	240	260

COMMENT

The data indicate S^{35}-chlorpromazine to be widely distributed throughout the areas of the brain, which show differential patterns of accumulation, especially the hypothalamus, which exhibited continual accumulation during the experimental period. Whether this specific localization influences the pharmacological response to subsequent doses of chlorpromazine is not known, but the problem affords a background for much speculation and further experimentation. A secondary effect of the influence of initial accumulations on the distribution of repeated doses of chlorpromazine is indicated by the reduced activity in the thalamus and cerebellum on the third and fourth days. Currently, this is being investigated by electric stimulation techniques. The distribution of activity in the lipid fraction of the liver reached a maximum after two doses and remained fairly constant thereafter. The activity found in the protein fraction was only 5% to 10% of that found in the lipid fraction and increased steadily. The ratio of these activities increased also, indicating a true increase in protein-bound S^{35}-chlorpromazine or its metabolic products. Whether the accumulation observed here could ultimately impair liver function is not known, but previous studies [3] have indicated a rapid turnover of S^{35}-chlorpromazine in liver and other tissues following a single dose. Examination of plasma activity indicated S^{35}-chlorpromazine to be carried by the lipid components, none being found in precipitable plasma protein. It is not improbable that the S^{35}-chlorpromazine was loosely bound to the protein or lipoproteins and was removed completely by the drastic extraction procedure.

The effect of chlorpromazine on the phospholipid turnover in the various anatomical regions of the brain is most interesting, particularly the reduced activity in the cortex of animals receiving the 50 mg/kg. dose. These animals exhibited a completely quiescent state for nearly 24 hours, whereas the rats receiving the 25 mg/kg. dose were inactivated for only a short time. The increased activity in the hypothalamus at the end of 24 hours may be due to changes in tissue permeability induced by the chlorpromazine. Preliminary studies substantiate this interpretation. The reduced activity (compared with controls) observed after 48 hours may be due to some inhibitory effect of metabolic products of the accumulated chlorpromazine, but at present this is conjecture. Except for slight degrees of inhibition, the results found in the cerebellum and thalamus are presently uninteresting. Although difficult to interpret because of incomplete separation of the pons, medulla, and mesencephalon, the increased activity

exhibited, 8%-17%, is worthy of further investigation.

The implications of some of the phospholipid changes observed here are wide-reaching. The inhibition of ATPase and cytochrome oxidase and the uncoupling of oxidative phosphorylation † may be related to the changed phospholipid turnover demonstrated in this study. However, it is difficult to relate in vitro observation with in vivo studies, especially since we have found S^{35}-chlorpromazine to be readily taken up by tissue slices and homogenates, making interpretation of data in terms of media concentration difficult.

SUMMARY

Chlorpromazine accumulates in the anatomical areas of the brain at different rates and to varying degrees. The turnover of phospholipids of the brain is reduced by chlorpromazine, especially in the cortex and the hypothalamus.

These studies were sponsored by a grant from the Smith, Kline & French Laboratories and the English Fund of the Hahnemann Medical College and Hospital of Philadelphia.

Miss Nancy Inforzato gave technical assistance.

REFERENCES

1. Moyer, J. H.; Kinross-Wright, V., and Finney, R. M.: A. M. A. Arch. Int. Med. **95**:202, 1955.

2. Van Ommen, R. A., and Brown, C. H.: J. A. M. A. **157**:309, 1955.

3. Wase, A. W., and Christensen, J.: Acta pharmacol. et toxicol., to be published.

4. Abood, L. G.: Proc. Soc. Exper. Biol. & Med. **88**:688, 1955.

5. Grenell, R. G.; Mendelson, J., and McElroy, W. D.: A. M. A. Arch. Neurol. & Psychiat. **73**:347, 1955.

† References 4 and 5.

Experience with the Surgical Treatment of Psychomotor Epilepsy

Early Results

J. A. PICAZA, M.D.
and
J. GUMÁ, M.D., Habana, Cuba

INTRODUCTION

The relationship of the temporal lobe to the mechanism of production of the great majority of psychomotor epilepsies is a well-established fact. Even though the mechanism of production of the psychomotor attack is not entirely clear, Penfield [1] (1950) revealed that a number of affected patients may be improved, or even made completely free of seizures, following the removal of the so-called "epileptogenic focus." More recent reports seem to corroborate these findings (Bailey,[2] 1951; Green,[3] 1951; Maspes,[4] 1953; Krayenbhul,[5] 1953; Guillaume,[6] 1953; Paillas,[7] 1953, and their associates).

Definite conclusions on the surgical treatment of the epilepsies probably should not be derived in less than 10 years of follow-up. However, experience with early results in what appears to be a useful procedure is welcome. This paper is a report on our observations.

MATERIAL

The data comprising this report come from the outpatient clinic practice, including both service and private patients. Only one patient was in a mental hospital; 34 were selected for surgery. These patients had seizures, probably due to a focal temporal-lobe dysrhythmia.

All patients had had seizures appearing recurrently for at least 1 to 38 years, and intensive medical treatment had been given during not less than one, and usually for many, years. Attacks in all patients were of the psychomotor type, preceded or not by aura. Complete neurological examination was followed by serial EEG recording at different times and under activation by sleep, thiopental (Pentothal), or pentylenetetrazol (Cardiazol). The attacks were observed under artificial reproduction, and only cases in which consistent dysrhythmia was revealed in several EEG's were taken to surgery. Encephalography was performed in all such cases, and angiography when needed. With a few exceptions, in which operation was performed with local anesthesia, most patients receive a general light thiopental-nitrous oxide-oxygen anesthesia. Secobarbital (Seconal), 0.10 gm., was the only premedication given. Electrocortigrams were taken from the whole exposed area of the temporal lobe and neighboring cortex. A locally made electrocorticograph set, following Penfield and Jasper's principles, was used, attached to a regular eight-channel Grass machine. During the electrocorticography activation was carried out with thiopental, pentylenetetrazol, or electricity (Grass 4A Stimulator). All cases have been periodically followed by clinical observation and repeated EEG's since the operation, over a period ranging from 8 to 48 months. Only five cases had less than one year's follow-up. These 34 patients underwent 35 craniotomies, with one operative death.

In the selection of these cases for surgery, all data have been gathered, and the indication for surgery arose from an understanding of the etiopathogenesis of the case. The approach has been total in scope, and not based on isolated features.

CRITERIA FOR EVALUATION

In the evaluation of the therapeutic results obtained in the attacks in these cases, we have followed the criteria of Penfield and Steelman,[8] as follows:

Received for publication Aug. 26, 1955.
Read before the National Neuropsychiatric Congress, Habana, Cuba, Jan. 29, 1955.
Neurosurgical Service, Hospital Mercedes (Dr. Picaza). Department of Electroencephalography, Hospital Mercedes (Dr. Gumá).

Failure

Group 0: No change in the attacks following the operation or the seizures made worse

Group I: Slight but definite improvement

Worth-while improvement.

Group II: At least 50% improvement in the form either of a decrease in the number or in the severity of fits

Success

Group III: Almost complete freedom of attacks (not more than one or two seizures)

Group IV: Complete freedom of attacks

Patients in Groups 0 and I believe the treatment was not a worth-while therapeutic procedure; it, thus, should be considered a failure. Patients belonging to Group II feel happy with the improvement obtained with the operation; thus the procedure should be considered worth while. Patients in Group III and IV represent the successes.

In this work, we have paid attention only to the effects of surgery in the attacks. The modifications obtained with the operation in the psychosocial behavior of these patients will be material for a separate report.

TABLE 1.—*Effects of Surgery on the Attacks of Psychomotor Epilepsy*

Group			No. of Cases
0	No improvement	Failure: 24%	5
I	Slight improvement	....	3
II	More than 50% improvement (accepted by patients and physician)	Improvement: 18%	6
III	One or two attacks before stopping	Success: 58%	7
IV	No more attacks	....	13
	Total	100%	34

RESULTS

The effects of surgery upon the attacks in this series of patients are shown in Table 1. These general results are dependent on many factors, mainly related to the way in which cases are selected for surgery, the etiopathogenesis, and the surgical technique. These general results seem to be of little importance without the analysis of at least several of the most important factors.

All cases showed psychomotor attacks. Five of them with a history of only grand mal seizures proved, under conditions of artificial production, to have a short psychomotor status before going into a major convulsion.

Seventeen types of aura were recorded, thus leaving any possible relationship to the results without statistical significance. The five cases showing confusion as an aura were treated successfully. The most frequent aura found was an abdominal sensation, either alone (four cases) or associated with a feeling of fright (eight cases); the results in the last cases were equally distributed as to failure and success.

In a large proportion of cases the possible etiology of the attacks was assumed from the clinical history and the surgical findings. It is notable that benefit was obtained in all four cases due to postnatal trauma.

All eight patients who had a neoplasm revealed no evidence of pressure, and the seizure were their only symptom. This fact could account for the high frequency of success in stopping their attacks that followed operation (six were in the success group; one was improved, and one was a failure). The only case that did not show improvement was found to have a diffuse astrocytoma, and the patient died after the operation. This was the only operative mortality in the entire group. All other tumors were small and apparently were completely removed.

Patients who had had meningoencephalitis showed as unpredictable results as the large group of unknown etiology, although an important number of patients revealed worthwhile improvement.

Analysis of our material reveals that when the preoperative study consistently shows a unilateral focus in several EEG's, either in the anterior or in the medial temporal area, and usually of spike or sharp-wave quality, operation is frequently followed by success. Patients with bilateral temporal dysrhythmia, either asynchronous or asymmetric, have not been successfully treated and the surgical results have been poor. However, a number of patients with a focus extending to the neighboring lobes had worth-while results.

In all but five cases histologic studies of the removed tissue were carried out. Atrophy was evident from the presence of an increased number of glial cells, the diminished

number of neurones, or the presence of damaged neurones, and sometimes thickening of the piarachnoid. These patients in general obtained good results from surgery. The two cases in which a large fibrous scar was found, one post-traumatic and the other post-encephalitic, resulted in complete surgical success.

The neoplasms found in the eight patients had the following histologic classification:

	No. of Cases
Fibrillary astrocytoma	4
Meningioma	1
Ganglioneuroma	1
Astrocytoma diffusum	1
Oligodendroglioma	1

The two failures were in a patient with an astrocytoma diffusum, who died, and a patient with a calcified oligodendroglioma of the posterior left temporal area, in whom the focus was found involving the speech area.

TABLE 2.—*Relation of Surgical Technique and Operative Results*

	Lobectomy				
Group	Radical*	Not Radical†	Cortectomy‡	Removal of Tumor§	Removal of Tumor and Cortex
0	1	1	2	..	1
I	1	1	1	..	..
II	..	3	1	1	..
III	3	1	1	..	2
IV	5	2	3	1	3
	10	8	8	2	6

* Including cortical focus, tip of temporal lobe, and uncus-amygdaloid and hippocampus.
† As with radical lobectomy, but not including uncus, amygdaloid, and hippocampus.
‡ Removal of the epileptogenic cortex, but not including tip of temporal lobe or deep structures.
§ Removal of tumor but not of cortex.

It should be remarked that a case with a small, partially cystic ganglioneuroma of the periamygdaloid area was treated by removal of the neoplasm only. After the operation the attacks disappeared, and the EEG became normal in less than six months, remaining so for the last three years. When no definite histologic findings were present, surgical results were irregular.

In Table 2 are noted the various surgical procedures employed in the treatment of this series. It is obvious that the incidence of success was higher in cases in which more radical procedures were carried out. Conservative, not radical, procedures, such as cortectomy, although useful in a number of cases, more frequently fail to alleviate the seizures. In two patients undergoing radical lobectomy the operation resulted in complete failure, and both revealed a bilateral synchronous asymmetric temporal focus, with postoperative persistence of abnormal activity in the opposite temporal lobe. In cases of brain tumor, although improvement occasionally results from the removal of the neoplasm only, success apparently is more frequently achieved by removing the lesion with the adjacent epileptogenic cortex.

COMMENT

The general principles for the surgical treatment of psychomotor epilepsy laid down by Penfield and Bailey have been used by various authors, with personal variations. Most of their reports are of short-period observations. An attempt has been made to

TABLE 3.—*General Results with Surgical Treatment of Temporal Lobe Epilepsy by Various Authors*

Author	Penfield et al.	Guillaume et al.	Paillas, Gastaut, et al.	Picaza et al.	Bailey and Gibbs	Green et al.	Maspes and Marossero	Krayenbuhl et al.		
Locality	Montreal	France	France	Habana	Chicago	United States	Turin, Italy	Zurich	Total No.	Percentage
Follow-up period, yr.	10	4	4	4	3	2½	2	1 to 2	..	..
No improvement										
Group 0	7	2	4	5	3	..	..	..	..	..
Group I	4	9	11	3	8	11	4	8	79	30
Definite improvement										
Group II	13	11	2	6	..	..	3	3	38	14
Excellent improvement										
Group III	13	17	5	7	8	..	..	..	..	..
Group IV	14	33	9	13	1	12	6	8	146	56
Totals	51	72	31	34	20	23	13	19	263	100

gather their results, following the same criteria of evaluation (Table 3). For a chronic disease, such as epilepsy, which is apt to show spontaneous remissions, probably only Penfield's report could be considered reliable. However, taking into consideration the personal variations, a review of Table 3 reveals a similarity in results obtained by all authors. Moreover, the over-all result shows over 50% success, a figure that probably would not be reached by any medical treatment of these cases.

The low operative mortality has been corroborated by all authors (Penfield, one; Bailey, two; Green, none; Guillaume, none; ours, one). For a meticulous, usually long-lasting, intracranial procedure, this mortality should be considered reasonably low.

In our experience, little, if any, value in regard to prognosis could be deduced from the study of the symptomatology; however, from the etiologic standpoint, traumatic lesions have a better prognosis. It is probable that in a number of cases of unknown etiology the patient actually may have suffered a brain compression at birth through the mechanism suggested by Earle and associates.[10]

Unilateral temporal dysrhythmia in the EEG, sometimes extending to the surrounding lobes (frontal, occipital, or parietal), has shown more frequent success. On the other hand, bilateral temporal discharges of any kind have very seldom yielded a worthwhile result.

When a gross lesion was found macroscopically or histologically at operation, the possibility of obtaining good results was greatly increased. The more radical surgical procedures, including removal of the superficial focus as revealed by the electrocorticogram, the temporal tip, the amygdaloid nucleus, the uncus, and the anterior third of the hippocampus, have given the most constant good results. In cases of neoplasms, removal of the lesion with the adjacent epileptogenic cortex has been more likely to be successful.

According to the above-mentioned findings, the best surgical possibilities would be in those cases fulfilling most of the following requirements:

1. Psychomotor epilepsy
2. Clinical or roentgenologic evidence of unilateral cerebral damage
3. Unilateral medial or anterior temporal lobe discharge
4. Histopathologic findings at operation
5. Radical operation procedure

Of the 20 cases of our series in which the results have been classified as successful, 17 fulfill at least four of these given requirements. The only unsuccessful case of the group revealed the presence of a bilateral asynchronous dysrhythmia in the EEG.

SUMMARY

The therapeutic results of temporal lobe surgery in 34 cases of psychomotor epilepsy during four years are reviewed. The early conclusions concerning this treatment by various authors are evaluated.

NOTE:—After this paper had been finished, there came to our hands the publication by Percival Bailey,[11] in which the author reviews 95 cases, 34 of which came from Dr. Green's series. Although the material was not suitable for addition to Table 3 of our paper, the results in general were very similar to ours. In cases of unilateral focus, 64% could be called successful; in cases of bitemporal focus, only 23% were successful. In no case was the illness worse after operation.

Dr. Francis M. Forster reviewed the manuscript.

Calle I, #506, Vedado.

REFERENCES

1. Penfield, W., and Flanigin, H.: Surgical Therapy of Temporal Lobe Seizures, Arch. Neurol. & Psychiat. **64**:491-500, 1950.

2. Bailey, P., and Gibbs, F. A.: The Surgical Treatment of Psychomotor Epilepsy, J. A. M. A. **145**:365-370, 1951.

3. Green, J. R.; Duisberg, R. E. H., and McGrath, W. B.: Focal Epilepsy of Psychomotor Type: A Preliminary Report of Observations on Effects of Surgical Treatment, J. Neurosurg. **8**: 157-172, 1951.

4. Maspes, P. E., and Marossero, F.: Considérations sur 28 cas d'épilepsie temporale opérés, Rev. neurol. **88**:578-580, 1953.

5. Krayenbuhl, H.; Hess, R., and Weber, G.: Enseignements de l'électroencéphalographie et corticographie et thérapeutique chirurgicale d'apres 21 cas d'épilepsie temporale traités par excision corticale ou par lobectomie, Rev. neurol. **88**:564-567, 1953.

6. Guillaume, J.; Mazars, G., and Mazars, Y.: Indications chirurgicales dans les épilepsies dites "temporales," Rev. neurol. **88**:461-501, 1953.

7. Paillas, J.-E.; Gastaut, H.; Bonnal, J., and Vigouroux, R.: Corrélations anatomo-électrocliniques dans l'epilepsie temporale: À propos des résultats obtenus chez 38 opérés, Rev. neurol. **88**: 568-574, 1953.

8. Penfield, W., and Jasper, H.: Epilepsy and the Functional Anatomy of the Human Brain, Boston, Little, Brown & Company, 1954.

9. Penfield, A., and Steelman, H.: The Treatment of Local Epilepsy by Cortical Excision, Ann. Surg. **126**:740-762, 1947.

10. Earle, K. M.; Baldwin, M., and Penfield, W.: Incisural Sclerosis and Temporal Lobe Seizures Produced by Hippocampal Herniation at Birth, A. M. A. Arch. Neurol. & Psychiat. **69**:27-44, 1953.

11. Bailey, P.: Betrachtungen über die chirurgische Behandlung der psychomotorischen Epilepsie, Zentralbl. Neurochir. **14**:195-206, 1954.

Thinking Disturbances in Delirium

MAX LEVIN, M.D., New York

Formal disturbances in thinking have been studied in schizophrenia (most notably by Bleuler) and in brain trauma (Kurt Goldstein and others), but their occurrence in delirium has received little attention.

The basic thinking disturbance in delirium is disorientation. The special characteristics of delirious disorientation were explained by Hughlings Jackson, and I have considered them elsewhere.*

This paper is divided into three sections. The third section deals with the inability of the delirious man to name the physician's vocation on command when he can name it spontaneously, a phenomenon of special interest from the standpoint of Jackson's views on neural function.

DISTURBANCES OF ASSOCIATION

This section deals with the disturbances of association which Bleuler demonstrated as one of the basic symptoms of schizophrenia. These disturbances are not confined to schizophrenia but occur in other psychoses as well. They abound in delirium, and the following cases are typical.

CASE 1.—Man aged 51. While at the Harrisburg State Hospital, in a bromide delirium, the patient was asked what place this was, and he replied "Philadelphia." (What part of Philadelphia?) "The northeastern part." (How do you know that?) "I can tell from the way the sun shines into my room" (meaning the angle of the sunbeams).

This case is a pure example of illogical thinking. The angle of the sunbeams does have to do with the points of the compass, but it indicates the direction of the house, and not the part of the city.

Received for publication Sept. 2, 1955.

* References 1 to 3.

CASE 2.—Man, aged 55; bromide delirium. In April he was asked the date, and he replied that it was the first week in December. (In other words, Christmas will soon be here?) "No, that's already gone." (Then this can't be the first week in December.) "Then it must be the second week in December."

This example compares favorably with the gags of our better comedians, showing that the faulty logic that underlies psychotic thinking also forms the basis of some types of humor.

CASE 3.—Woman, aged 52; bromide delirium. The patient was admitted to the hospital on July 6, in her 10th day of delirium. Two examples are taken from this case.

(*a*) On July 9 she said it was the middle of August. She knew she was in hospital and remembered correctly that on July 4 she had been at home. (About how long ago was July 4th?) "It was last week." (If July 4th was last week, how could it now be August?) "August comes after July." This answer was given with sincerity and conviction, and she obviously thought it responsive to the question.

(*b*) On Aug. 4, while still in delirium, she gave the date correctly. (How long have you been here?) "About a month." I reminded her that throughout the previous month she had always named the month as August, and I asked, "If you've been here a month, and it's been August all this time, how could it now be only the fourth of August?" She replied, "Well, the fourth of August *is* August." Here, again, as in the previous example, she replied with a statement which in itself is impeccable, but whose responsiveness to the question is illusory.

The two instances reveal an inability to see a discrepancy, and, too, when the discrepancy has been pointed out, an inability to see that the answer offered in explanation thereof is no answer at all. It only seems to be an answer. In the attempt to explain the discrepancies her associations were derailed into pseudorelevancies.

CASE 4.—Woman, aged 51; bromide delirium. When asked the date (Feb. 15), the patient replied,

"I believe, the way I hear them [nurses] talk, it's Easter, isn't it?" When asked what the nurses had been talking about, she said it was about eggs, fried and soft-boiled. Thus, a false inference was drawn from a nurse's remark about the breakfast menu. There was a syllogism: "Easter has to do with eggs; they are talking about eggs; it therefore must be Easter."

Thus it is clear that delirium can produce an association disturbance indistinguishable from that of schizophrenia.

From the standpoint of ease in investigation it is far easier to study faulty thinking in delirium than in schizophrenia. Blocking and other interferences make it hard to get close to a schizophrenic. It is exasperating, when the patient says something that suggests a disorder of association, to strive in vain to get him to explain what he had in mind when he said it. By contrast, the delirious patient (if he is not also schizophrenic) is in good rapport and will talk freely.

FAILURE TO "MAKE CONNECTIONS"; MORBID LACK OF PERPLEXITY

While the mind is infinitely complex and unpredictable, one can in some situations predict, more or less, what a man will do or think in response to a stimulus. When one says "Thank you" to a man, the chances are that he will reply "You're welcome." When an American hears the phrase "the White House," he is pretty certain to think of the house of the President. When a healthy man is asked his address or telephone number, he will give it correctly. In such situations, if a man failed to respond properly, one would wonder whether something was wrong.

Much of our behavior is the manifestation of conditioned reflexes. Learning a language or a telephone number means acquiring new conditioned reflexes. A conditioned reflex means that a "connection" has been established between the substrate of an image and that of a verbal or other response. In a state of reduced mentation there may be a weakening of these connections. The clearest example is the failure of memory in senile dementia. When an old man who has trod the streets of his neighborhood for many years now gets lost on his way home from the grocery store, it is because complex conditioned reflexes have been weakened; the connections that take part in the formation of a pattern (in this instance, a topographical pattern) have lost their firmness.

As an illustration of failure of memory in states of reduced mental power, I give an example from my own experience. Although I got out of the Army in 1946, I remember my Army serial number as I do my own name. One morning in 1955 I woke at 6 o'clock and, while musing in bed, tried to recall the number. There came to mind the number O5-107108. I knew at once this was not right. I reflected that if this had been my number, I would from the start have noticed the sequence of 107 and 108, a memory aid. Trying in vain to recall the number, I fell asleep again for an hour. Later in the morning, at 10 o'clock, the incident flashed through my mind, and the correct number came to me instantly, O-517108.

In sleep there is paralysis of the highest cerebral centers ("inhibition," Pavlov called it), and some of it may linger for a while after waking. This is the explanation of postdormitial paralysis and diplopia.† Failure to remember a number, in the example just given, is likewise a paralytic phenomenon, indicating that a stable "connection" is now in abeyance. Predormitial and postdormitial paralysis can be serious. If a man drives a car when very sleepy, he may fail to "make connections"; he may fail to recognize and react to the many signals a driver must be ready for. Likewise, on going into or coming out of coma there is reduced mentation; the dullness of a man emerging from an epileptic fit is an example.

That the delirious man thinks and "makes connections" poorly is obvious. The essence of delirium is the inability to grasp new and complex situations as they arise.‡ This is the basis of delirious disorientation. I shall refer to only one manifestation of this

† References 4 and 5.

‡ References 3 and 6.

loss of thinking power, viz., the patient's failure to be perplexed by things that would perplex a healthy man. Here are two examples.

CASE 5.—A schoolteacher, on recovery from a barbiturate delirium, recalled this scene in her psychosis: "I seemed to fly [figuratively] so quickly from one place to another. One minute I'd be here [the Hospital], and the next minute I'd think I was in Shippensburg [her home town]." This did not puzzle her at the time, and it was only after she got well that she marveled at this quick shift of scene.

CASE 6.—After recovery from a bromide delirium a woman recalled a scene from her psychosis: She thought she was on a transatlantic vessel in mid-ocean, where she saw a large pole sticking up from the water. She felt no astonishment at the time.

Physicians are aware of morbid perplexity as a psychiatric symptom. They must also be aware of morbid lack of perplexity. Delirium is said to be a dream-like state. Morbid lack of perplexity is one of its dream-like features. In dreams the strangest things will happen without causing any astonishment. The capacity to notice that something is wrong or out of place—an eye for discrepancy—is one aspect of intelligence. The skill of a diagnostician depends in part on his ability to spot the features of a case that clash with a given tentative diagnosis. In the cases cited in the first section the patients were unaware of discrepancies in their reasoning.

INABILITY TO NAME PHYSICIAN'S VOCATION ON COMMAND

The delirious patient, being disoriented for person, may be unable to name the physician's vocation on command. In spite of this he may spontaneously and unwittingly address the physician as "Doctor." Thus, he will greet his physician with "Good morning, Doctor," and he freely uses such expressions as "Yes, Doctor" and "Thank you, Doctor." There have been several amazing instances in which the patient addressed me as "Doctor" in the very sentence in which he confessed his inability to name my vocation. Thus, one patient, when asked what my work is, replied in embarrassment, "I wouldn't know, Doctor—is it painting and decorating?" Another complained bitterly, "I'm just so unstrung, Doctor"; she was then immediately asked what my work is, and replied, "Why, I *did* know it yesterday, but I forgot. I *did* know it yesterday, Doctor."

This phenomenon, which seems so paradoxical, is exactly like one seen in some cases in motor aphasia and other cerebral disorders, in which the patient fails to perform on command tasks which spontaneously he performs with ease. An aphasic may be unable to name an object shown him, and yet the word may come to his tongue spontaneously, as when he asks to borrow your pencil. To take an example often used by Jackson, an aphasic who cannot say "No" on command may say it in reply to a question calling for a negative answer; and he will shout "No!" under emotional stress, as when his child is about to creep too close to the fire.

Jackson classified utterances into three categories: (*a*) Emotional utterance is that which expresses an emotion, as when a man shouts a warning to his child. (*b*) Propositional speech states a proposition relatively free of emotion, as when he says "No" to a question calling for a negative answer. (*c*) Voluntary utterance is when he says "No" as a sheer act of will, because you have asked him to. Jackson showed that these three categories, in the sequence just given, are arranged in order from most automatic (least voluntary) to least automatic (most voluntary). Emotional utterance is most automatic, because the words "come out without thinking." When a child is in danger, the father does not have to stop to think what to say; shouts of warning come to his tongue automatically. Propositional speech is not as automatic as that, but it is more automatic than voluntary utterance. In much of our propositional speech we are not acutely conscious of our words; much of the time we are conscious of meanings and intentions more than of words. By contrast, when a man says "No" only be-

cause you have asked him to, his utterance is a studied and calculated act, a pure act of volition.

The naming of the physician's vocation may be compared with the utterance of "No." When the patient in distress pleads "Help me, Doctor," the analogy is with the emotional "No." When he names the doctor's vocation on command, the analogy is with the voluntary "No." The vocative "Doctor" in ordinary conversation, as in "Good morning, Doctor," is comparable to the propositional "No." Here the analogy is not perfect, but it is good enough for our present purpose. In the scale of automaticity the vocative "Doctor" stands between the emotional and the voluntary "Doctor."

The analogy of "Doctor" and "No" extends even to those striking instances in which the patient unwittingly addresses you, his physician, as "Doctor" in the very sentence in which he confesses he does not know your vocation. This, too, one sees in the aphasic. The aphasic, unable to say a word on command, may say it unwittingly at the very moment he is giving voice to his failure. A patient, striving to say "No" on command, may at last give up and cry in despair, "No, I can't say it." Or, when asked to repeat the word pencil, he may after an effort say helplessly, "I just can't say pencil."

This phenomenon—the inability to say "No" on command when one can shout it on emotion, and the comparable inability to name the physician's vocation on command when one spontaneously addresses him as "Doctor"—may seem paradoxical. But it is no more so than the fact that pupils may contract on accommodation but not to light. Physicians see no paradox here, for they know that there is not just one pathway for pupillary constriction, but two. The two pathways, one for constriction to light, the other for constriction on accommodation, join at the point where the final common path begins. Interruption of just one of the pathways will cause selective loss of constriction, as in the Argyll Robertson pupil. It is the same with higher functions. There is not just one pathway for "No," but as many as there are stimuli capable of eliciting that word. That is to say, the pathways for this or any other word or verbal expression are without number. For the sake of simplicity, I shall speak of three pathways, for emotional, propositional, and voluntary "No," respectively. If we disregard the final common path, the three pathways occupy different levels, the "voluntary pathway" being the highest. The "emotional pathway" is so far down that it can keep on functioning undisturbed by the lesion, higher up, of a motor aphasia.

The pattern that follows on paralysis of the highest cerebral centers Jackson called "reduction to a more automatic condition," for the highest (most voluntary) functions are lost, while the lowest (most automatic) remain. Delirium offers many examples of "reduction to a more automatic condition."

We physicians have our eye trained for differences. For example, we study the differential diagnosis of "organic" and "functional" disease. This is important, but it is not enough. We must also look for similarities of things that superficially look different. A shrew and a whale have a lot in common: they are mammals. Hughlings Jackson, who clarified the distinction between a highest-level fit (the "ordinary" grand mal) and a middle-level fit (what we today call a Jacksonian fit), was equally assiduous in studying the principles that apply to both of them, in common.

If there is one theme that runs through Jackson's writings more than any other, it is that the levels of the nervous system differ in complexity only, and not in their fundamental constitution and kind of organization. He stressed that the highest cerebral centers, no less than the lowest, obey the laws of reflex action.[7] From this standpoint the phenomenon described in this section is, I believe, of interest. We have to consider a "mental" disease, delirium, and a "focal organic" disease, manifested by aphasia. The mechanism of speech is complex, but not as

complex as that of mentation. It is therefore striking that the delirious patient's inability to name the physician's vocation on command when he spontaneously addresses him as "Doctor" should find so exact a parallel in the comparable phenomenon in aphasia.

350 Central Park West (25).

REFERENCES

1. Levin, M.: Delirious Disorientation: The Law of the Unfamiliar Mistaken for the Familiar, J. Ment. Sc. **91**:447, 1945.

2. Levin, M.: Delirium: A Gap in Psychiatric Teaching, Am. J. Psychiat. **107**:689, 1951.

3. Levin, M.: Perseveration at Various Levels of Complexity, with Comments on Delirium, A. M. A. Arch. Neurol. & Psychiat. **73**:439, 1955.

4. Levin, M.: The Pathogenesis of Narcolepsy, with a Consideration of Sleep-Paralysis and Localized Sleep, J. Neurol. & Psychopath. **14**:1, 1933.

5. Levin, M.: Diplopia in Narcolepsy, Arch. Ophth. **29**:942, 1943.

6. Levin, M.: Toxic Delirium Precipitated by Admission to Hospital, with Remarks on the Diagnosis of Incipient Delirium, J. Nerv. & Ment. Dis. **116**:210, 1952.

7. Levin, M.: Reflex Action in the Highest Cerebral Centers: A Tribute to Hughlings Jackson, J. Nerv. & Ment. Dis. **118**:481, 1953.

News and Comment

GENERAL NEWS

Association for Research in Nervous and Mental Disease.—At the 35th annual meeting of the Association for Research in Nervous and Mental Disease, held in New York on Dec. 9 and 10, 1955, the following officers were elected for the year 1956.

President	Dr. Harry C. Solomon
First vice-president	Dr. Stanley Cobb
Second vice-president	Dr. Wilder Penfield
Secretary-treasurer	Dr. Rollo J. Masselink
Assistant secretary	Dr. Lawrence C. Kolb

American Academy of Neurology.—Special coures in nine different neurological subjects will be presented by a selected faculty at the April, 1956, meeting of the American Academy of Neurology in St. Louis, on April 23, 24, and 25. Three courses will be given each day: Neuropathology, Infectious Diseases in Neurology, Clinical Electroencephalography and Electromyography, Convulsive Disorders, Neurologic Disorders in Infancy and Childhood, Neurochemistry, Injuries to the Nervous System, Current Advances in Neurology. Neurophysiology will require two days. In addition, the Academy will also present a Course for General Practitioners.

For details, write Mrs. J. C. McKinley, executive secretary, 3501 E. 54th St., Minneapolis 17.

Afferent Nerves to Clarke's and the Lateral Cuneate Nuclei in the Cat

CHAN-NAO LIU, Ph.D., Philadelphia

It is generally stated that Clarke's nucleus extends from the upper thoracic to the upper lumbar portion of the spinal cord and that it is a relay nucleus between the hindlimb and lower trunk and the cerebellum. The lateral cuneate nucleus is likewise believed to be a relay nucleus between the forelimb and the cerebellum. In an earlier study (Liu,[18] 1954) on transneuronal degeneration, it was found that Clarke's nucleus receives an extensive supply from the dorsal roots of all body parts except the neck, and that the dorsal root terminals show an extensive overlap within the nucleus. These observations indicated that Clarke's nucleus is supplied by dorsal root afferents from the forelimb, as well as from the trunk and the hindlimb.

The aims of the present study were (1) to determine the distribution and termination of representative dorsal roots from various body parts (neck, trunk, tail, and limbs) to the nucleus of Clarke and the lateral cuneate nucleus of von Monakow, and (2) to determine whether these two nuclei, although anatomically discontinuous, are so organized that they might be considered as a single functional relay system, with the possibility of interaction and integration of afferents from adjacent body parts.

Received for publication Aug. 15, 1955.

Department of Anatomy, University of Pennsylvania School of Medicine.

This investigation was supported by research grant PHS B-221 from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, U. S. Public Health Service.

MATERIAL AND METHODS

Twenty adult cats were used. In each animal, one dorsal root was cut extradurally and proximal to the dorsal root ganglion. In this way dorsal roots were cut at all spinal levels (cervical, thoracic, lumbar, sacral, and coccygeal). A total of 18 dorsal roots were severed. The animals were anesthetized with intraperitoneal pentobarbital (Nembutal), and aseptic conditions were maintained throughout the operative procedures. The dorsal roots to be cut were localized in relation to the dorsal spinal processes by the anatomical diagram of the vertebra and spinal cord of the cat, as described by Krieg and Groat.[12] The desired dorsal root was exposed by enlarging the intervertebral foramen from the lateral side of the vertebral column. With clear visualization of the root, one point of a pair of fine scissors was placed in the gap between the dorsal and the ventral root and the dorsal root cut extradurally. This procedure was found to produce no damage to the spinal cord, such as usually occurs after laminectomy and opening of the dura. The animals were killed by a perfusion fixation method (Koenig and associates[11]) four to seven days after dorsal root section. The entire brain and the spinal cord were removed with all spinal nerves attached, so that the dorsal root section, as well as the different spinal segments, could be identified. The point of entrance of the severed dorsal root and representative levels of the spinal cord in the animal were sectioned and stained by the Nauta and Gygax[20] technique, a method which selectively impregnates degenerated axoplasm. This method has been used with excellent results in experimental studies of the efferent connections of the striate cortex in the rat (Nauta and Bucher[19] and is especially useful for following disintegrating nerve fibers to their synaptic termination. The parts of the central nervous system prepared for histological examination from each experimental animal included (1) a segment of cord at the level of entrance of the severed dorsal root, (2) alternate segments of the cord above the severed root entrance to the level of the medulla oblongata, (3) alternate segments of the cord below the severed dorsal root to the level of the cord where no degenerated fibers could be identified, and

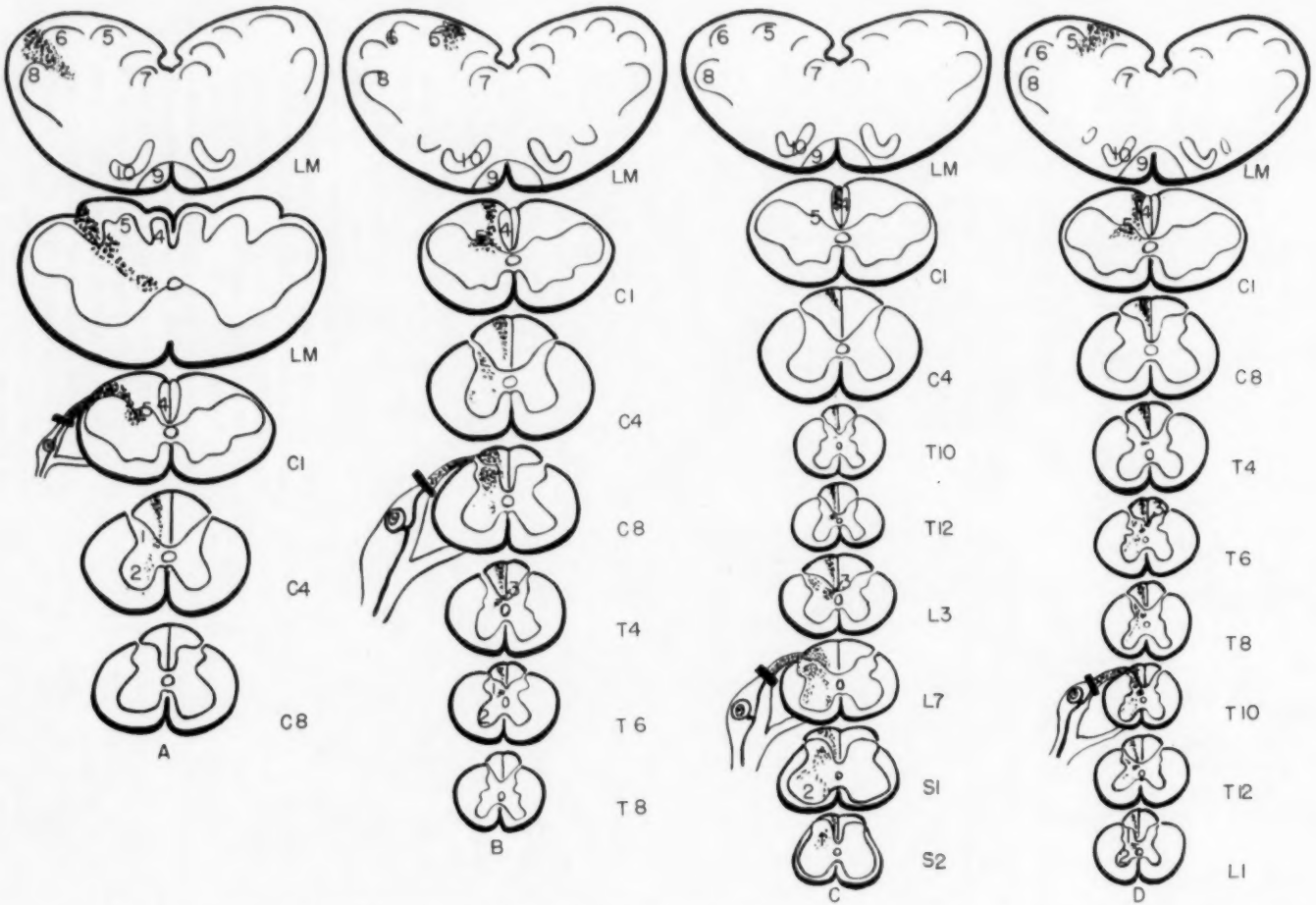


Fig. 1.—Schematic representation of different levels of the neuraxis to show the distribution of degenerated fibers following severance of representative dorsal roots. The degenerated fibers are shown as dots. (*A*) Dorsal root C1 was cut. (*B*) Dorsal root C8 was cut. (*C*) Dorsal root L7 was cut. (*D*) Dorsal root T10 was cut. *1* indicates dorsal horns; *2*, ventral horn; *3*, Clarke's nucleus; *4*, nucleus gracilis; *5*, nucleus cuneatus; *6*, lateral cuneate nucleus; *7*, nucleus of XII nerve; *8*, radix spinalis V (nucleus and tract); *9*, pyramid; *10*, inferior olivary nucleus; *LM*, lower medulla; *C*, cervical spinal segments; *T*, thoracic spinal segments; *L*, lumbar spinal segments; *S*, sacral spinal segments.

(4) the entire medulla oblongata. Degeneration was studied and plotted entirely from cross sections.

OBSERVATIONS

Four to seven days following the section of dorsal roots, the intramedullary portion of the degenerated root fibers could be clearly identified. These degenerated fibers, selectively impregnated with silver, appeared as black droplets, irregular masses, and beaded strands (Glees and Nauta[8]). It was found

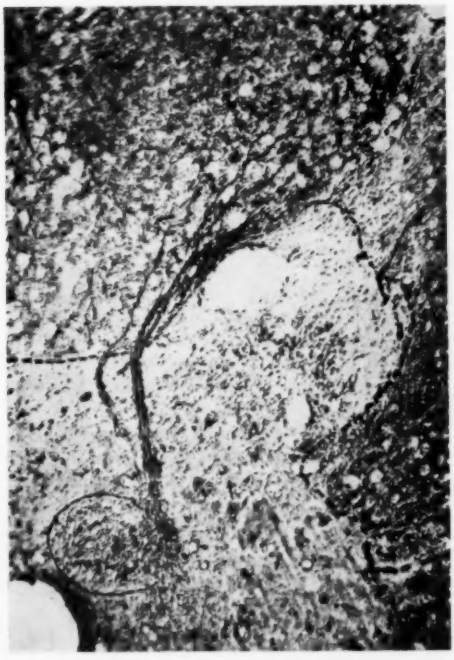


Fig. 2.—Photomicrograph of a cross section of the spinal cord of the cat at the level of T10, showing the degenerated fibers as fascicles running from the dorsal funiculus to the gray matter. Dorsal root T10 was cut unilaterally, and animal was killed five days later. For clarity, the boundaries of the gray matter are outlined by a broken line, and Clarke's nucleus is circumscribed in a similar fashion. Reduced to 59% of mag. × 75.

that the amount of degenerated fibers was greatest in the cord at the level of entrance of severed dorsal roots (Fig. 1*A, B, C, D*). This degeneration gradually diminished in the cord above and below the level of root sections. The distribution of the degenerated fibers was determined both in the white matter and in the gray matter of the spinal cord. In the white matter, the degenerated fibers were limited to the dorsal funiculus. These degenerated fibers were arranged in a band, lying immediately dorsal to the dorsal horn at the level of root entrance. This band of degenerated fibers contains the fragments of ascending and descending branches from the entering dorsal root fibers. At more cranial levels, this band gradually shifts dorsomedially and diminishes in size. The reduction in size is due to a gradual termination of fibers or a reduction in the caliber of fibers after giving off collaterals or both (Lloyd and McIntyre[14]). After section of any dorsal root, no degenerated fibers could be identified cranially beyond the levels of the nucleus gracilis, nucleus cuneatus, and nucleus cuneatus lateralis (Fig. 1) of the medulla oblongata. At levels below the root entrance, the degenerated fibers were distributed irregularly in the dorsal funiculus. These degenerated fibers extend in the cord for four to six segments below the level of root entrance, with the exception, of course, of the most caudal roots. No degenerated fibers, either ascending or descending, were found in the lateral or ventral funiculi of the spinal cord following the severance of any dorsal root.

In the spinal cord at the level of the severed root, many small fascicles of degenerated fibers were seen passing from the dorsal funiculus into the gray matter. These fascicles, collaterals from the degenerated longitudinal fibers of the dorsal column, passed ventrally and terminated in the gray matter at the level of their origin (Fig. 2).

All fibers of the dorsal roots terminating in the spinal cord entered the gray matter in this manner. The number of collaterals was found to be greatest in the segment of the spinal cord at which the root entered.

The degenerated fibers entering the gray matter soon leave the fascicles and ramify between the nerve cell bodies. Many fibers in the gray matter were traced to cell soma and dendrites and were found to end there in the form of blackened droplets; these are interpreted as true terminal degeneration

(Fig. 3). The degenerated fibers were most numerous at the level of root entrance. They were distributed in the ipsilateral dorsal horn as follows: most degeneration in the nucleus proprius cornudorsalis, less in the nucleus posteromarginalis, and least in the substantia gelatinosa (terminology from Mettler [16]). There are also a fair number of degenerated fibers at the junction of the dorsal and ventral horns and in the ventral horn proper, on or near the motor cells. Also, at this level, a few degenerated fibers were found to pass via the dorsal white commissure and to terminate among the cells stated to be limited to spinal cord segments T1-L4 (Rexed [23]).

Degenerated fibers and terminals were found in this nucleus following representative dorsal root section of sacral, lumbar, thoracic, and cervical dorsal roots (Table). The pattern of dorsal root distribution to this nucleus can be seen in Figure 1. Dorsal root fibers terminating in Clarke's nucleus from the coccygeal, sacral, and lower lumbar dorsal roots (L5-L7) come from collaterals of the ascending branches of the dorsal root fibers. The cervical roots supplying Clarke's nucleus come from collaterals of descending

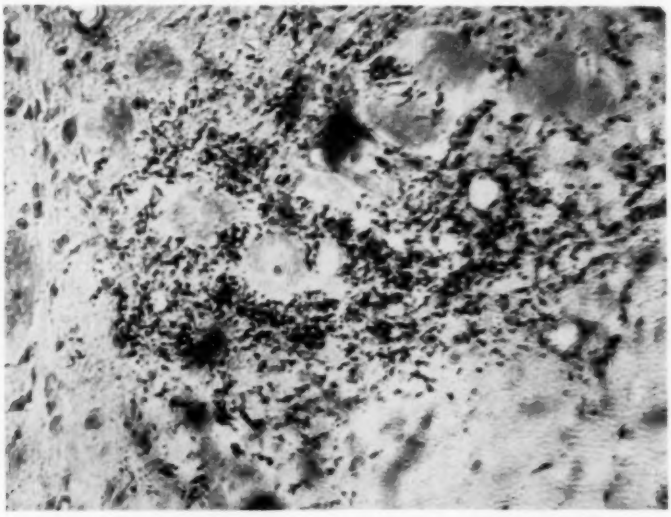


Fig. 3.—Photomicrograph of cells in Clarke's nucleus at L3 showing the degenerated fibers of dorsal root L7 distributed in the dendritic field and on the cell bodies. The dorsal root was cut four days before killing the animal. Reduced to ⅔ of mag. × 260.

of the dorsal horn of the contralateral side. The degenerated fibers in the segments of the cord above and below that of the sectioned dorsal root were distributed to gray matter similarly, but in reduced amount.

In the following paragraphs, the distribution of dorsal roots to Clarke's nucleus and the lateral cuneate nucleus will be described in considerable detail.

Clarke's Nucleus.—Clarke's nucleus consists of a bilateral longitudinal column of large multipolar cells, many of which are as large as the somatic motor cells. This columnar nucleus is located at the base of the dorsal horns near the central canal and is usually branches of the dorsal root fibers (C5-C8). The dorsal roots of spinal segments T1-L4 supply Clarke's nucleus via collaterals from both ascending and descending branches of the dorsal root fibers. The dorsal roots of one side of the body supply only Clarke's nucleus of the same side. These dorsal root collaterals arise in fascicles, of varying size, from the dorsal funiculus and run ventrally in this funiculus on the medial side of the dorsal horn. They usually enter Clarke's nucleus directly without passing through other parts of the dorsal horn (Fig. 2). These collaterals were found to be distributed throughout this nucleus, both in the circumscribed dendritic field and on the nerve cell

*Amount and Intramedullary Distribution of Different Dorsal Root Fibers to the Lateral Cuneate and Clarke's Nuclei as Determined by a Degeneration Method**

Dorsal Root Cut	Lateral Cuneate Nucleus †								Clarke's Nucleus																			
	Caudal				Cranial				Thoracic																Lumbar			
	M	V	L	D	D	L	V	M	1	2	3	4	5	6	7	8	9	10	11	12	13	1	2	3	4
C1	1+	1+	1+	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
C2	1+	1+	1+	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
C3	1+	1+	1+	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
C4	...	1+	...	...	...	1+	1+	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
C5	...	1+	...	...	...	1+	1+	...	1+	1+	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
C7	1+	...	...	...	...	1+	...	...	1+	1+	1+	1+	1+	...	...	...	...	...	...	...	...	...	...	...	...	...
C8	1+	...	1+	1+	...	...	...	...	1+	1+	1+	1+	1+	1+	...	...	...	...	...	...	...	...	...	...	...	...
T1	1+	...	...	1+	...	...	...	...	2+	2+	1+	1+	1+	1+	1+	...	...	...	...	...	...	...	...	...	...	...
T4	...	...	1+	...	1+	...	...	1+	1+	1+	2+	3+	2+	1+	1+	1+	...	...	...	...	...	...	...	...	...	...
T5	...	...	1+	...	1+	...	...	1+	1+	1+	1+	2+	3+	2+	1+	1+	1+	...	...	...	...	...	...	...	...	...
T10	...	...	...	...	...	...	...	...	...	...	1+	1+	1+	1+	1+	1+	2+	3+	2+	1+	1+	1+	...	...	...	...
L1	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1+	1+	1+	1+	1+	2+	3+	4+	3+	2+	1+	...
L2	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1+	1+	1+	1+	1+	2+	3+	4+	3+	2+	...
L6	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1+	1+	1+	1+	2+	3+	4+	5+	4+	...
L7	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1+	1+	1+	2+	3+	4+	6+	4+	...
S1	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1+	1+	1+	2+	3+	2+	...
Ca1	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1+	1+	...
Ca4	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1+	...

* The relative density of degeneration from a single dorsal root section is indicated by the number of plus (+) signs.
† The different portions of the lateral cuneate nucleus are indicated by the following letters: M, medial portion; V, ventral portion; L, lateral portion; D, dorsal portion. The spinal cord levels of Clarke's nucleus are numbered.

bodies (Fig. 3). The blackened droplets on the cell bodies are considered to be degenerated terminals (Szentàgothai and Albert [26]).

The amount of degenerating fibers to Clarke's nucleus was greatest from the dorsal roots of the hindlimb (Fig. 4) and trunk. The dorsal roots of the forelimb, tail, and neck supply many fewer collaterals to the nucleus. It was found by plotting the degeneration after section of different dorsal roots that there is a considerable overlap in the distribution to this nucleus. For example, dorsal root T10 supplied all but the rostral and caudal ends of Clarke's nucleus (Table 1). The rostral projection of T10 was found to overlap the caudal distribution of C8 (Table and Fig. 1), while the caudal distribution of T10 overlaps the rostral termination of S3 (Table). The distributions of the dorsal roots from the different body parts are shown diagrammatically in Figure

Fig. 4.—Photomicrograph of a cross section of spinal cord L3, showing the greatest amount of degeneration in Clarke's nucleus five days after unilateral section of dorsal root L7. Reduced to 60% of mag. × 75.

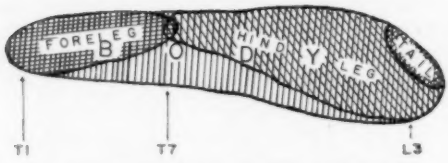


Fig. 5.—Schematic drawing to show the distribution of the dorsal roots from different body parts to Clarke's nucleus. Note that the dorsal roots of the trunk occupy the whole nucleus and that there is a slight overlapping of the dorsal roots from the foreleg and the hindleg. Spinal levels of the nucleus are indicated by T11 and T7 (thoracic) and L3 (lumbar).

5. The overlapping of dorsal root fibers from different body parts is striking. It is to be noted that the trunk region occupies all the nucleus, while the tail, hindlegs, and forelegs are confined to specific regions. However, it can also be seen that the hindlimb region overlaps the tail region.

Lateral Cuneate Nucleus.—The lateral cuneate nucleus consists of a bilateral aggregation of large multipolar cells which are similar to those of Clarke's nucleus (Hollis,[10] 1884; Sherrington,[24] 1890; Pass,[21] 1930; Ferraro and Barrera,[7] 1935). This nucleus is located in the lower medulla at the level of the 10th and 12th cranial nerve nuclei. It is just lateral to the cuneate nucleus, as its name implies. Degenerated fibers and terminals were found in this nucleus after section of spinal dorsal roots C1-T5 (Table). The dorsal root fibers terminating in this nucleus are derived from collaterals of ascending branches of the dorsal roots that run in the funiculus cuneatus. The collaterals from the dorsal roots T5-C1 terminate in both the lateral cuneate and the cuneate nucleus, while, in addition, dorsal roots C1, C2, and C3 supply collaterals to the spinal accessory nucleus and the tractus and nucleus solitarius. The collaterals from T5-C4 branch at right angles from the longitudinal fibers of the fasciculus cuneatus; the medial collaterals enter the gray matter of the cuneate nucleus, and the lateral ones enter the lateral cuneate nucleus (Fig. 6). The collaterals of C1, C2, and C3 enter more directly the lateral cuneate nucleus and send their longest collaterals medially to the cuneate nucleus (Fig. 7).

The collaterals to the lateral cuneate nucleus are distributed in the circumscribed dendritic field and on the cell bodies. The blackened droplets on the cell bodies are considered to represent degeneration of true terminals, although some of them may represent degeneration in the dendritic field. The distribution of the dorsal roots to the lateral cuneate nucleus was found on the basis of maximum degeneration to be arranged as an oblique spiral lamella, with fibers from the highest spinal root (C1) occupying the caudal pole and those from the lowest spinal root (T5) occupying the cranial pole. The oblique spiral lamella was arranged around a central

Fig. 6.—Photomicrograph of section from lower medulla oblongata to show the degenerated fibers in left lateral cuneate nucleus (*LCN*) and left cuneate nucleus (*CN*) following severance of left dorsal root T5. The degeneration time was five days. Reduced to 60% of mag. × 110.

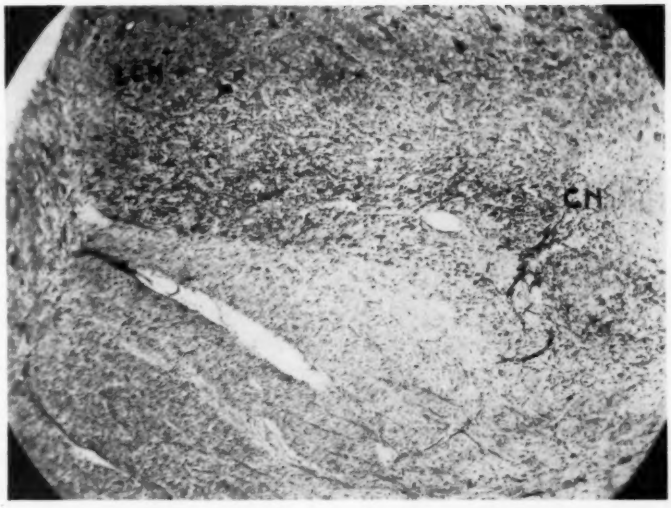
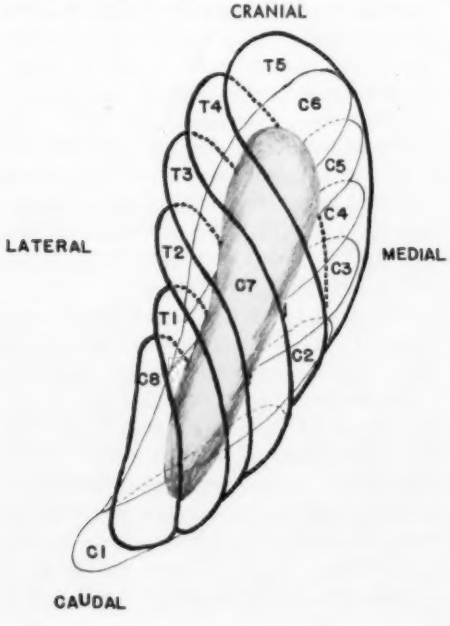


Fig. 7.—Photomicrograph of section of the lower medulla oblongata to show the degenerated fibers in the left lateral cuneate nucleus (*LCN*) and cuneate nucleus (*CN*) following severance of left dorsal root C1. The degeneration time was five days. Reduced to ⅔ of mag. × 75.

core of the nucleus, the latter being chiefly supplied by dorsal root collaterals from C7. The distribution of dorsal roots rostrocaudally on the dorsal surface is as follows: T5 terminates in the rostral pole and dorsolateral surface; T4, T3, T2, T1, and C8 terminate in more caudal and dorsomedial parts, and C7 terminates on the dorsomedial border near the caudal pole, as well as in the core of most of the nucleus, as described above. The distribution of dorsal roots on the ventral surface, starting from the caudal end of the nucleus and progressing rostrally, is as follows: C1 occupies the caudal pole and the ventrolateral part; C2, C3, C4, C5, and C6 occupy successively more ventromedial parts (Fig. 8). However, there is considerable overlap among the successive dorsal roots. For example, on the dorsal surface T2 overlaps with T5 cranially and with C8 caudally. On the ventral surface C4 overlaps cranially with C6 and with C1 caudally; all dorsal roots overlap near the periphery of the nucleus with C7, which supplies all of the core of the nucleus except at the extreme poles.

Fig. 8.—Schematic reconstruction based on the maximum number of degenerated fibers in the lateral cuneate nucleus following severance of different dorsal roots (C1-T5).



COMMENT

The experiments reported in this paper are chiefly concerned with the distribution and termination of afferent fibers of the spinal dorsal roots to the nucleus of Clarke and the lateral cuneate nucleus of von Monakow. That Clarke's nucleus is activated by proprioceptive fibers of the spinal dorsal roots has been determined by selective electrical stimulation of the Group I fibers (stretch

afferents) of dorsal roots and muscle nerves and by recording the evoked potentials in the dorsal spinocerebellar tract (Grundfest and associates,[9] Lloyd and McIntyre,[14] Mountcastle and associates [18]).

The new anatomical observations reported in this paper are due chiefly (1) to the extensive series of selective single dorsal roots which were sectioned, and (2) to the staining technique of Nauta and Gygax,[20] which selectively stains the degenerating dorsal root axons, permitting a determination not only of their intramedullary course but also of their site of termination. The discussion of these new observations and their interpretations will be dealt with as follows: (1) Clarke's nucleus and (2) the lateral cuneate nucleus.

Clarke's Nucleus.—Clarke's nucleus is a bilateral column of multipolar cells located in the mediobasal part of the dorsal horn of the spinal cord segments T1-L4 (Rexed [23]), and each column of cells sends its axons ipsilaterally in a superficial pathway in the dorsal part of the lateral funiculus of the spinal cord to terminate in the cerebellum (Bruce,[4] Beck,[1] Brodal and Jansen,[3] Yoss [28]). This nucleus is generally stated in textbooks of neuroanatomy and neurology to receive dorsal root afferents from the hindlimb and the lower trunk. The present experiments have shown that in the cat Clarke's nucleus receives ipsilateral dorsal root afferents from all the spinal nerves except the upper cervical ones (C1-C4). Thus, the proprioceptive impulses from all body parts—tail, hindlimb, trunk, and forelimb, with the exception of head and neck—pass through Clarke's nucleus. The proprioceptive disturbances of both fore- and hindlimbs which follow section of the dorsal spinocerebellar tract at the spinal level of C3-C4 were reported by Ferraro and Barrera.[7] From the symptoms following section of the dorsal spinocerebellar tract at this level, they suggested that there might be dual cerebellar connections for the cervical segments of the spinal cord, one via the dorsal spinocerebellar tract and one via the lateral cuneate nucleus. Our experiments give an anatomical explanation of their physiological findings, as we found that the dorsal spinocerebellar tract is a relay system for the whole body except the upper neck and head.

Pass [21] sectioned the dorsal roots of the spinal segments L7, C6, and C7, respectively, in three cats. He followed the myelin degeneration by the Marchi technique and reported that only L7 innervates Clarke's nucleus. He found that the descending branches of the bifurcating intramedullary fibers of C6 and C7 descend in the comma tract of Schultz for only two to three segments in the spinal cord. In our experiments the most rostral cervical dorsal root supplying Clarke's nucleus was C5 (Table). This root had descending intramedullary fibers in the dorsal funiculus for five segments and supplied Clarke's nucleus at spinal segments T1 and T2. It was further found that dorsal roots C7-T1 had descending branches which supply Clarke's nucleus six segments below the level of spinal root entrance, while T4-T10 and L2 sent descending branches to Clarke's nucleus four segments and two segments, respectively, below the level of root entrance. Our observations on the course and termination of the descending branches of spinal dorsal roots to Clarke's nucleus are at variance with the general statement that descending intramedullary dorsal root fibers descend for only two to three segments in the spinal cord. However, we found that only Clarke's nucleus was supplied as much as four to six segments below the level of root entrance and that the other nuclei of the dorsal horn received terminals only two to three segments below the level of root entrance.

The observation that some dorsal root fibers (C7-T1) supply as many as six segments of Clarke's nucleus through collaterals of descending intramedullary branches reveals a considerable overlapping in the central distribution of afferent fibers of the dorsal roots. This overlapping of distribution of descending branches is, however, less extensive than that which occurs from ascending afferent fibers of some dorsal roots (Table). It was found that L7 supplied as

much as eight segments of Clarke's nucleus. The afferent supply to Clarke's nucleus is much more extensive than heretofore reported by anatomical or physiological studies. Pass [21] sectioned two dorsal roots (L7, S1) and reported degeneration in Clarke's nucleus for only four segments (L4-L1). In closer agreement with our observations are the physiological findings of Lloyd and McIntyre.[14] They selectively stimulated the Group I fibers of muscle nerves and found that large stretch afferents from dorsal root L7 supplied six segments of Clarke's nucleus (L4-T12). The less extensive afferent supply to Clarke's nucleus reported by both Pass and Lloyd and McIntyre is probably due to the fact that the number of terminals to Clarke's nucleus from L7 is greatly reduced in upper segments (T12-T10; Table).

The extensive overlapping of afferent fibers of certain dorsal roots in their termination in Clarke's nucleus by means of both collaterals of ascending and descending branches (Fig. 4 and Table) clearly indicates that afferent stimuli via a single dorsal root, such as T10, from the trunk could interact at the level of Clarke's nucleus with appropriately timed afferent stimulation from the forelimb and the hindlimb. A limited interaction of muscle afferents at Clarke's nucleus was obtained by recording from the dorsal spinocerebellar tract upon stimulation of the peroneal and hamstring nerves (Grundfest and Campbell,[9] Morin and Haddad,[17] Sprague [25]).

Lateral Cuneate Nucleus.—The lateral cuneate nucleus is synonymous with the external cuneate nucleus, nucleus of von Monakow, magnocellular nucleus of the posterior funiculus, outer restiform nucleus, and accessory cuneate nucleus (Brodal [2]). Ferraro and Barrera [7] proposed the name of nucleus of Clarke-Monakow in honor of Clarke, who first described the nucleus anatomically [5] (1868), and Monakow (1885, 1891), who first established experimentally its efferent connection to the cerebellum. The nucleus is located in the lower portion of medulla at the level between the 10th and the 12th cranial nerve nucleus. The cells are larger than those within the cuneate nucleus. They are similar to the cells of Clarke's nucleus (Hollis,[10] Sherrington,[24] Pass,[21] Ferraro and Barrera [7]). This nucleus is just lateral to the cuneate nucleus, as its name implies. Its axons project to the cerebellum via the inferior cerebellar peduncle (Monakow, 1885; Bruce [4]; MacNalty and Horsley [15]; Brodal and Jansen,[3] and many others).

The afferent supply of this nucleus via collaterals and terminals of dorsal roots has been studied by Ranson and associates,[22] Pass,[21] Escolar,[6] and Ferraro and Barrera.[7] Ranson and associates and Escolar sectioned the first three cervical dorsal roots in the cat and reported that the lateral cuneate nucleus is supplied by these dorsal roots. Pass [21] sectioned dorsal roots C6 and C7, respectively, in two cats and found that these two cervical nerves terminate at this nucleus. None of these studies indicated the pattern of distribution or the extent of the dorsal root supply. We have found, by cutting representative single dorsal roots in the cat, that all cervical and the upper five thoracic dorsal roots supply the lateral cuneate nucleus (Table). Furthermore, we have been able by the technique of Nauta and Gygax [20] to determine the distribution of each dorsal root supplying the nucleus (Fig. 8) and the characteristics of its terminal endings within this nucleus. Our findings in the cat are in agreement with the observations (Ferraro and Barrera [7] and Walker and Weaver [27]) in the monkey, that the cervical and upper thoracic dorsal roots supply this nucleus. We did not, however, find the same pattern of laminated distribution of the different dorsal roots reported by them. They reported a single ventrolateral and dorsomedial lamination, with the upper cervical dorsal roots ventrolateral and the lower cervical and thoracic ones dorsomedial. The pattern of distribution of the dorsal roots supplying this nucleus in the cat is arranged as a spiral oblique lamella, with the 7th cervical dorsal root occupying the core and the first cervical dorsal root forming the ventrolateral caudal pole, while the lowest thoracic dorsal root, T5, supplies the dorsolateral rostral pole

(Fig. 8). There is some overlapping of adjacent dorsal roots. The difference in the distribution of the dorsal roots in the cat and monkey may be attributed to species differences, but it should be pointed out that Ferraro and Barrera [7] did not determine the degeneration of single dorsal roots and had to employ a less critical stain (Marchi).

The observations in the present paper on the origin of the dorsal roots supplying the lateral cuneate nucleus and Clarke's nucleus force a modification of the general statement that the lateral cuneate nucleus is the afferent relay for the neck and forelimb, while Clarke's nucleus is the corresponding relay for the lower limb and trunk. Clarke's nucleus, which receives stretch afferents (Lloyd and McIntyre [11]), is now known to receive dorsal roots from all of the body except the neck. The lateral cuneate nucleus, although the fibers have not been determined to be derived from stretch afferents, is supplied by dorsal roots from the neck, forelimb, and upper trunk. It is apparent from the Table that dorsal roots C1-T5 supply both the lateral cuneate nucleus and Clarke's nucleus. This overlapping in distribution, when considered in light of the similarity of cell types of the two nuclei (Hollis,[10] 1884; Cajal, 1911) and the same pattern of terminal connections, supports the earlier suggestions that the lateral cuneate nucleus is the cranial extension of Clarke's nucleus. In fact, Hollis has reported that he was able to show a continuity of these two cellular masses, although the number of cells in the cervical cord were few in number. Therefore, we visualize these nuclei as two anatomically distinct relay nuclei between the periphery and the cerebellum, but as a single functional system with the possibility of interaction of afferents from adjacent body parts.

SUMMARY

The distribution of 18 representative dorsal root afferents supplying the lateral cuneate nucleus and Clarke's nucleus was determined by degeneration methods in cats. It was found that Clarke's nucleus receives its dorsal root supply from all body parts except the head and upper neck, and the distribution of dorsal roots to this nucleus showed an extensive overlap.

The lateral cuneate nucleus receives its dorsal root supply from the neck, forelimb, and trunk. The distribution of such dorsal roots was found to be in the form of a spiral oblique lamella. Overlapping of adjacent dorsal roots in this nucleus was also observed. Dorsal roots C5-T5 supply both the lateral cuneate nucleus and Clarke's nucleus. Interaction and integration of proprioceptive activity at these relay nuclei are suggested.

Drs. W. W. Chambers and J. M. Sprague made valuable suggestions in this study.

REFERENCES

1. Beck, G. M.: The Cerebellar Terminations of the Spino-Cerebellar Fibers of the Lower Lumbar and Sacral Segments of the Cat, Brain **50**:60-98, 1927.

2. Brodal, A.: Die Verbindungen des Nucleus cuneatus externus mit dem Kleinhirn beim Kaninchen und bei der Katze, Ztschr. ges. Neurol. u. Psychiat. **171**:167-199, 1941.

3. Brodal, A., and Jansen, J.: Beitrag zur Kenntnis der spino-cerebellaren Bahnen beim Menschen, Anat. Anz. **91**:185-195, 1941.

4. Bruce, A.: Note on the Upper Termination of the Direct Cerebellar and Ascending Antero-Lateral Tracts, Brain **21**:374-382, 1898.

5. Clarke, J. L.: Researches on the Intimate Structures of the Brain, Phil. Tr. Roy. Soc. London **158**:263-331, 1868.

6. Escolar, J.: The Afferent Connections of the 1st, 2nd and 3rd Cervical Nerves in the Cat, J. Comp. Neurol. **89**:79-92, 1948.

7. Ferraro, A., and Barrera, S. E.: Posterior Column Fibers and Their Termination in Macacus Rhesus, J. Comp. Neurol. **62**:507-530, 1935.

8. Glees, P., and Nauta, W. J. H.: A Critical Review of Studies in Axonal and Terminal Degeneration, Monatsschr. Psychiat. u. Neurol. **129**:74-91, 1955.

9. Grundfest, H., and Campbell, B.: Origin, Conduction and Termination of Impulses in the Dorsal Spino-Cerebellar Tracts of Cat, J. Neurophysiol. **5**:275-294, 1942.

10. Hollis, W. A.: Researches into the Histology of the Central Grey Substance of the Spinal Cord and Medulla Oblongata, J. Anat. & Physiol. **18**:62-65, 1884.

11. Koenig, H.; Groat, R. A., and Windle, W. F.: A Physiological Approach to Perfusion-Fixation of Tissue with Formalin, Stain Technol. **20**: 13-22, 1945.

12. Krieg, W. J. S., and Groat, R. A.: Topography of the Spinal Cord and Vertebral Column of the Cat, Quart. Bull. Northwestern Univ. M. School **18**:265-268, 1944.

13. Liu, C. N.: Study of the Innervation of Clarke's Nucleus in the Cat, Anat. Rec. **118**:326, 1954.

14. Lloyd, D. P. C., and McIntyre, A. K.: Dorsal Column Conduction of Group I Muscle Afferent Impulses and Their Relay Through Clarke's Column, J. Neurophysiol. **13**:39-54, 1950.

15. MacNalty, A. S., and Horsley, V.: On the Cervical Spino-Bulbar and Spino-Cerebellar Tracts and on the Question of Topographical Representation in the Cerebellum, Brain **32**:237-255, 1909.

16. Mettler, F. A.: Neuroanatomy, Ed. 2, St. Louis, C. V. Mosby Company, 1948.

17. Morin, F., and Haddad, B.: Afferent Projections to the Cerebellum and the Spinal Pathway Involved, Am. J. Physiol. **172**:497-510, 1953.

18. Mountcastle, V. B.; Covian, M. R., and Harrison, C. R.: The Central Representation of Some Forms of Deep Sensibility, A. Res. Nerv. & Ment. Dis., Proc. **30**:339-370, 1952.

19. Nauta, W. J. H., and Bucher, V. M.: Efferent Connections of the Striate Cortex in the Albino Rat, J. Comp. Neurol. **100**:257-286, 1954.

20. Nauta, W. J. H., and Gygax, P. A.: Silver Impregnation of Degenerating Axons in the Central Nervous System: A Modified Technique, Stain Technol. **29**:91-93, 1954.

21. Pass, I. J.: Anatomic and Functional Relationships of the Nucleus Dorsalis (Clarke's Column) and of the Dorsal Spino-Cerebellar Tract, Arch. Neurol. & Psychiat. **30**:1025-1045, 1933.

22. Ranson, S. W.; Davenport, H. K., and Doles, E. A.: Intramedullary Course of the Dorsal Fibers of the First 3 Cervical Nerves, J. Comp. Neurol. **54**:1-12, 1932.

23. Rexed, B.: A Cytoarchitectonic Atlas of the Spinal Cord in the Cat, J. Comp. Neurol. **100**:297-379, 1954.

24. Sherrington, C. S.: On Outlying Nerve Cells in the Mammalian Spinal Cord, Phil. Tr. Roy. Soc. London **181**:33, 1890.

25. Sprague, J. M.: Single Unit Activity in Spino-Cerebellar Tract in Cats, Fed. Proc. **10**:131, 1951.

26. Szentàgothai, J., and Albert, A.: The Synaptology of Clarke's Column, Acta morphol. **5**:43-51, 1955.

27. Walker, A. E., and Weaver, T. A.: The Topical Organization and Terminations of the Fibers of the Posterior Columns in Macaca Mulatta, J. Comp. Neurol. **76**:145-158, 1942.

28. Yoss, R. E.: Studies of the Spinal Cord: I. Topographic Localization Within the Dorsal Spino-Cerebellar Tract in Macaca Mulatta, J. Comp. Neurol. **97**:5-20, 1952.

Psychosomatic Approach to Frontal Lobe Lesion

DAN G. HERTZ, M.D.
CARL H. FELLNER, M.D.
and
MILTON ROSENBAUM, M.D., Jerusalem

Much information has been garnered about the psychological and behavioral changes following surgery of the frontal lobes. However, it is rather difficult to make generalizations from this literature because of the differences in the material and contradictions in the conclusions drawn therefrom. There is agreement on a number of points. A certain amount of impairment of intelligence, and especially of abstract thinking, appears to be common. Above all, it seems clear that ablations of anatomically corresponding areas need not produce similar changes from patient to patient. The localization and extent of the structural damage alone is not sufficient to explain the resulting behavioral change. The patient's personality plays a paramount role and certainly has to be taken into consideration in order to understand the changes resulting from frontal lobe operation.

Patients usually selected for lobotomy are psychotics of comparatively long standing, or elderly people who hope for relief from intractable pain (and usually suffering also from incurable cancer), or persons who have had severe obsessive-compulsive states of many years' duration. In these persons the preoperative personality is often badly distorted, a condition which increases the task of understanding the behavioral changes appearing after operation. Therefore, we believe it is of interest to report the study of a patient who had been a well-adjusted, successful business man, apparently in good emotional health before frontal lobe surgery.

Received for publication Oct. 3, 1955.

From the Department of Psychiatry, Hebrew University-Hadassah Medical School.

At present, Professor of Psychiatry, Albert Einstein College of Medicine (Dr. Rosenbaum).

This study was made possible by a grant from the Scheider Fund.

REPORT OF A CASE

The patient was a 40-year-old married man, who was referred to the psychiatric department of the Hebrew University-Hadassah Medical School in December, 1954 (by Dr. A. Beller), because of behavioral changes following a brain operation done four years before. In 1950 he had developed an abscess of unknown origin in the left frontal lobe. A left transfrontal craniotomy and enucleation of the abscess was done (by Dr. Beller) at the Hadassah-University Hospital. His immediate postoperative behavior was similar to that in patients after a prefrontal leucotomy (lobotomy); confusion, dullness, and retardation were present for a few days, followed by laziness, irritability, and lack of interest. He was discharged from the hospital four weeks after the operation.

He was readmitted to the hospital for a recheck three months after the operation. An electroencephalogram showed a reduction in activity in the right frontal area and a moderate degree of abnormal slow activity in the left frontal area, compatible with the destruction of brain tissue on the right and with dysfunction of the left frontal area. Pneumoencephalography showed dilatation of the left lateral ventricle, mainly in the anterior portion.

The patient, who was the manager of a commercial office, had returned to work two months after the operation. There his behavior was unlike his old self; he took little interest in his business, did not keep regular office hours, and spent much time in useless conferences with acquaintances, treating them to refreshments. His judgment in business was poor, and he squandered a good deal of money. Despite these inefficiencies, he continued to work. Finally, in 1953, his wife had to assume the direction of his business, much against his wishes. Before the operation the patient had been a good and steady family man, but he began to go

around with many women. He became much too interested in a sports club, where he soon became a "big shot" because of his frequent contributions of money. For instance, at a time when he was already greatly in debt and when his wife did not know how to meet their business obligations, he donated 1000 £ to the sports fund.

Also there occurred changes in his sexual behavior. He became increasingly demanding toward his wife, insisting on intercourse several times a day, as well as at night. In addition, he masturbated frequently, and he continued to go out with many other women. It was the latter fact that finally brought him to our clinic. His wife had learned about his unfaithfulness, but she forgave him repeatedly after confessions and promises to behave in the future. Finally her patience gave out and she threatened to divorce him. As a last resort, they turned to their physician for help, and he referred them to the psychiatric department.

This man's developmental history was of primary importance in understanding his behavior. The patient was the youngest of six siblings. His mother died when he was 2 years old, and shortly thereafter his father was called up for service in the army. As a result, all of the patient's brothers and sisters were cared for by relatives. Mainly because of his youth, he was sent to an orphanage, where he remained until the age of 6 years. When the war was over, the father returned, remarried, and reclaimed the other children. He wanted to leave the patient at the orphanage but was forced by the authorities to take him home. The patient did not get along well with his stepmother, who forced him to do most of the chores at home and made him miss school in order to do housework. The patient did not adjust well at school and was said to be retarded. When he was 12 years old, his father died, and he was cared for by his older brothers. At the age of 15 years he started work as an office boy at a local branch of a commercial enterprise, and over the years he worked his way up to become manager and part-owner. He was a hard-working, conscientious, and successful businessman.

In 1945, at the age of 31, he married, after courting his wife for about two years. She came from a wealthy and established family and in his opinion was socially and culturally his superior. She had been engaged for a long time to a friend of the patient, with whom he competed for her favor. When this engagement was broken, she accepted him, and they were married three months later. Up to the time of the brain operation, their marriage was described as "ideal"; they were very well adapted to each other and quite happy. Two sons were born, now aged 9 and 6½ years.

At the time of writing (May, 1954) all physical, neurological, and laboratory examinations, including the electroencephalogram, were essentially normal.

Psychological tests included the Rorschach, Bellevue-Wechsler, Szondi, T. A. T., and Bender Gestalt. The intellectual level of the patient was above average; obviously, he had retained much of his intellectual efficiency (present I. Q. about 110). Situations in which he could use knowledge formerly acquired aroused intelligent responses. The brain damage did not influence seriously gestalt perception, as far as measured by the tests. Perception of the outer world was normal.

However, the Bellevue-Wechsler test revealed disturbances typical for organic brain impairment, mainly in the field of attention and in speed of intellectual performance. If given sufficient time, he was able to solve even complicated tasks satisfactorily. In spite of disturbances in the field of intellectual performance, there seemed to be no difficulty in solving problems of everyday life, as determined by these tests.

The patient comprehended socially accepted standards and identified with them. In new situations, especially if an emotional and original reaction was required, he was quite helpless. Sexual phantasies dominated his thinking and prevented the establishment of a constructive emotional relationship with the environment. He was much disturbed by sexual preoccupation and experienced feelings of guilt because of his behavior. No special childhood conflicts were found which could explain his sexual preoccupation.

According to the Szondi test, there was a strong urge to repress dependency needs. However, this repression had not been successful.

The psychodynamics of this case were formulated as follows: The behavioral and personality changes following the operation on the left frontal lobe, which in their totality had become maladaptive, were considered to be due to a number of factors. The structural frontal lobe damage was one factor. The anxiety resulting from inability to cope adequately with his problems was another factor. Ego defenses, previously successful, no longer functioned adequately to maintain adaptive behavior. The previously successful repression of feelings of inferiority and insecurity resulting from intense dependency longings was no longer maintained. There resulted an increase of anxiety, which, in turn, led to new defenses, which were regressive (primitive) and therefore maladaptive.

This patient had a most traumatic childhood with unfulfilled dependency needs and blows to his self-esteem, which he managed to repress but which somehow enhanced his strong drives for success and prestige. He married a woman toward whom he felt socially and culturally inferior, but he overcompensated in his usual way by proving himself adequate by his business success. This also masked his underlying dependency on his wife. Since his life had been built on strivings for success and prestige, his failure in this area following the operation was a severe emotional trauma. At this juncture a perceptive physician might have helped him to face the, for him, new problems and to handle them as realistically as possible. Since he was operating on his own, his ego strivings found a new outlet in spheres in which he could still prove to himself his worth and in which he felt he could be successful, namely, in sexual and in certain social areas. The sexual outlet not only provided him with success and achievement (in conquering women other than his wife) but also represented an acting out of hostility against his wife because of his obvious dependency on her. He tried to achieve social success by being generous and playing the role of the openhanded host and benefactor, of course, to the detriment of his family. It is also of interest to note that he devoted his efforts to a sports club; it was in this club that he had first found companionship and acceptance as a young man, gratifications that he could not derive from his parents.

When his wife threatened divorce, his deepest anxiety was aroused. This mobilized deeply repressed feelings of helplessness, rejection, and abandonment, undoubtedly originally associated with the early loss of his mother. Therefore the pathological sexual and social behavior also may have served as a defense against the emergence of this infantile separation anxiety.

A plan of treatment was outlined in accordance with our psychodynamic formulations. The patient was sent to the hospital not only for observation and study, but also to relieve the tense atmosphere in his home caused by his disturbed behavior. The therapeutic task was to establish a consistent warm and limit-setting doctor-patient relationship which would gratify the patients dependency needs without further blows to his self-esteem. The physician served as a model for identification, with the hope that the patient's impaired ego and superego functions would be strengthened. If successful, patterns of behavior consistent with reality might gradually replace maladaptive and neurotic ones.

The first stage of treatment was a three-week stay at the hospital, which enabled us to complete our studies and to build a firm relationship between the patient and one of us (D. G. H.). Originally the patient had agreed to consult the psychiatrist only because of pressure put on him by friends and family. Actually, he had come in the hope of gaining our support to justify his conduct as natural, especially his sexual behavior. He had to be helped to see the results of this conduct in true perspective. With the developing relationship with the therapist, he soon began to feel that here was one person who really tried to understand him

and who was ready to help him in a practical manner, i. e., by working out a detailed daily schedule. The patient was encouraged to adhere to this schedule as closely as possible.

After his discharge from the hospital he returned for daily interviews, lasting from half an hour to one hour. He was to bring all his problems for discussion with the therapist; also, the daily routine was discussed, and any failure in it was gone into. This stage lasted for about eight weeks. Thereafter the duration and frequency of the interviews were gradually reduced. At one point there was a two-week interval when the patient was not seen at all, and he began to revert to his former behavior. In this connection it is worth while noting that treatment after discharge from the hospital was complicated by pressure exerted by acquaintances who tried to influence him against attending the psychiatric clinic, telling him that this was not necessary, as he was not, and never had been, insane. However, the transference situation was already sufficiently strong to withstand this pressure.

The patient responded well to treatment. He began to take more interest in his work, appeared punctually at his office, and worked through the day conscientiously. He was able to cooperate better with his business associates and also to ask frankly for advice if he could not handle a situation himself. Now, five months after treatment was begun, he spends more time at home, looks after his family, has had no more sexual escapades, and the frequency of sexual intercourse with his wife has returned to the preoperative level. In addition, he has been able to ask for the return of some of his generous, but foolish and irresponsible, donations; actually, the 1000 £ from the sports fund was returned to him. At present he is being seen about once or twice a week, and the treatment situation has progressed into a third phase, in which interpretations are given and motivations clarified. Concurrently with the treatment as outlined above, the patient's wife entered into therapy with a psychiatric social worker. Case-work therapy was designed chiefly to give her a better understanding of the problems facing her husband and also to give her support and understanding in her own difficult position. At first she was seen once a week, but now only once every other week for one hour.

COMMENT

Personality changes after brain damage can in no case be understood in terms of the actual damage alone; a dynamic neuropsychiatric approach is required properly to understand and treat such patients. The impairment of intellectual and emotional (ego) functioning resulting from structural damage can upset the equilibrium of the patient in several ways: The habitual defense reactions of the patient can be disturbed, or even put out of action altogether; and/or the anxiety resulting from the patient's perception (conscious and unconscious) of the changes in his functioning may revive or reinforce previous repressed fears and anxieties. In consequence, greater demands are made on an already impaired defense mechanism (ego), and a vicious circle is set up. In order to regain equilibrium, new defense mechanisms come into play which are maladaptive or neurotic, or the patient regresses to a lower level of functioning, or there is a combination of the two forms of reaction.

It has become increasingly clear over the years that behavior cannot be interpreted solely as the result of damage to specific brain areas. That the attempt is still made to do so more frequently than not is a tribute to one of the primary laws of behavior, that man tends to satisfy his needs and desires with the least exertion. Physicians who know no other law represent for patients an anachronism; they encourage the dissipation of their patients' energies, to say nothing of their time.

In many if not the majority of cases of brain damage one cannot hope to rehabilitate the patient maximally without knowing what sort of person he was before he was damaged. This involves an exploration of

the developmental history, as well as the utilization of modern techniques of reasonably rapid psychological evaluation which have become available.

Surely, it is obvious that one could not have hoped to have understood this patient's "deterioration" without a knowledge of his childhood and young adulthood. For a time, when this information was not available, his behavior was attributed to "frontal lobe damage." Such superficial evaluation is more widespread than one likes to acknowledge; this course of least resistance—conserving the physician's energy—surely is responsible for much misery and invalidism. Such method cannot be justified on the basis of limitations of time unless this be a one-sided consideration only, since in the long run it represents wastage of not only the time, but the substance of the patient.

SUMMARY

The study is reported of a previously successful 40-year-old married man who suffered from personality changes after the removal of a left frontal lobe abscess. Postoperative behavioral changes are described and compared with those that occur after prefrontal leucotomy (lobotomy). It is postulated that this behavior cannot hope to be understood on the basis of what might be termed a purely neurological approach. The psychodynamics of the behavioral change and of the treatment are discussed.

News and Comment

ANNOUNCEMENTS

Training in Child Psychiatry.—Specialized training in child psychiatry is available in a number of member clinics of The American Association of Psychiatric Clinics for Children which have been approved as training centers by the Association. The training begins at a third-year, postgraduate level with minimum prerequisites of graduation from an approved medical school, an approved general or rotating internship, and a two-year residency in psychiatry, approved by the American Board of Psychiatry and Neurology. The majority of these clinics have also been approved individually by the American Board of Psychiatry and Neurology for a third year of training and for an additional year of experience.

This training is in preparation for specialization in child psychiatry, and especially for positions in community clinics devoted wholly or in part to the outpatient treatment of children with psychiatric problems. At the completion of training, attractive openings are available in all parts of the country. Fellows receive instructions in therapeutic techniques with children in outpatient settings which utilize the integrated services of the psychiatric clinic team. Most of the clinics have a two-year training period, although a few will consider giving one-year training in special cases.

Fellowship stipends are usually in line with U. S. Public Health Service standards, that is, approximately $3,600, as these stipends come mainly from the Public Health Service. Stipends sometimes are paid by state departments of mental health, the individual clinics, and occasionally communities paying for the training of psychiatrists engaging to work in these communities at the end of their training. Special arrangements may be made occasionally to supplement the stipends by taking on other responsibilities locally (e. g., part-time work with the V. A., consultation to social agencies, etc.). A limited number of training centers can offer higher stipends.

The office of The American Association of Psychiatric Clinics for Children acts as a clearing house for applicants. Application may be made through this office or directly to the individual clinics. In all cases, acceptance of applicants for training is by the individual training centers. For further information and for application forms, write to Miss Marion A. Wagner, Administrative Assistant, American Association of Psychiatric Clinics for Children, 1790 Broadway, Room 916, New York 19.

Behavioral and Electroencephalographic Effects of Hallucinogenic Drugs

Changes in Cats on Intraventricular Injection

BERT E. SCHWARZ, M.D.
KHALIL G. WAKIM, M.D.
REGINALD G. BICKFORD, M.B.
and
FRANK R. LICHTENHELD, M.D., Rochester, Minn.

Feldberg and Sherwood's* previous studies of the behavior of cats after the intraventricular injection of various drugs opened up a new method of investigation. By this technique they showed that drugs injected into this area of high pharmacologic sensitivity could evoke various complex behavioral responses and conditions resembling sleep, anesthesia, profound muscular weakness, catatonia, and convulsions. Their classification of the effects characterized by certain common features of reaction suggested further experiments in which, in addition to the effects of the drug alone, antagonisms of various chemicals within the central nervous system might be studied. Of particular interest to experimental psychiatry is the possible antagonism of lysergic acid diethylamide and serotonin. Previously, Gaddum [3] had shown the effect of such antagonism on smooth muscle. Woolley and Shaw [4] hypothesized that, if such an antagonism exists, it might be an important factor in schizophrenia. Other drugs of interest behaviorally are mescaline, adrenochrome, adrenolutin (1-methyl-3,5,6-indolestriol), and ergotamine.

Received for publication Oct. 10, 1955.

Fellow in Psychiatry, Mayo Foundation (Dr. Schwarz). Section of Physiology, Mayo Clinic and Mayo Foundation (Dr. Wakim and Mr. Bickford). Fellow in Surgery, Mayo Foundation (Dr. Lichtenheld). The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

* References 1 and 2.

METHOD

Three cats anesthetized with pentobarbital sodium were operated on. Their heads were fixed in a cat Horsley-Clark stereotactic instrument. Midline incisions were made, and the fascia and temporalis muscles were laterally deflected. A trephination was made 15 mm. anterior to the line of the external auditory meatus and 7 mm. to the right of the midline. After a tiny incision had been made in the dura mater, a polyethylene catheter with a No. 22 stainless-steel stylet was introduced perpendicular to the cortex, but on a 15-degree angle with the midline. As the catheter was being inserted, the stylet was frequently withdrawn until clear cerebrospinal fluid, which freely pulsated with respiration, was evident. At this point a Lucite ring 8 mm. in diameter and approximately 4 mm. in height was cemented with Acralite plastic. The cap was securely fastened to the skull by pouring liquid Acralite around the catheter and allowing it to harden. The catheter was then cut off approximately 1 cm. above the cortex and was connected to a solid stainless-steel stylet. The catheter and stylet were then covered under a Lucite cone screwed into the skull receptacle (Fig. 1). Postmortem examination demonstrated the patent catheters (Fig. 2*a* and *b*) in the right lateral ventricle in two cats; in the third cat the tip of the catheter was located in the third ventricle.

Fig. 1.—Cat with intraventricular catheter and electrodes in position.

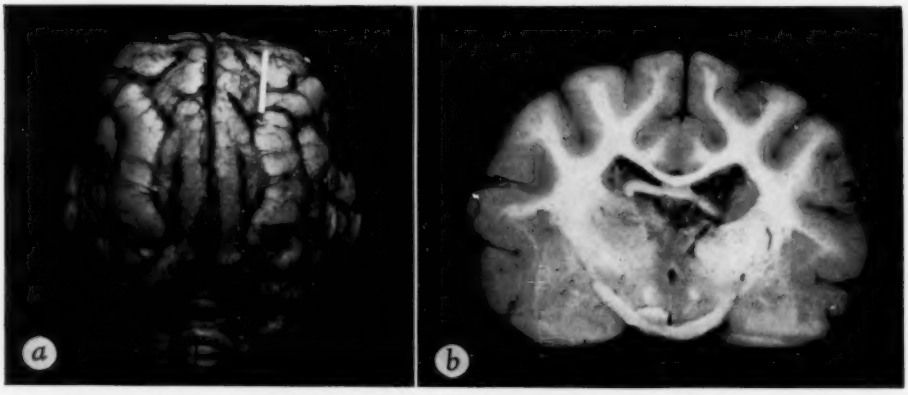


Fig. 2.—(*a*) Dorsal view of brain of cat, with catheter in place; (*b*) coronal section of brain of cat, showing position of catheter in right lateral ventricle.

As indicated in the electroencephalograms, six burr holes were made in the frontal, temporal, and occipital regions bilaterally. Electrodes (Fig. 3) connected to the central plug were placed extradurally in these locations and were permanently fixed with Acralite. Their location was confirmed by anteroposterior and lateral roentgenograms of the head. The fascia and muscles were then approximated in the midline with nonabsorbable surgical (silk) sutures, and the remaining area was smoothly covered with Acralite. Postoperatively, 0.5 cc. of a solution of procaine penicillin G was given for three days. The cats were fully alert and conscious when receiving the injections of the various drugs (Fig. 4). An intraventricular injection of 0.2 to 0.4 ml. of Tyrode's solution or isotonic solution of sodium chloride was given as a control measure to each cat before any of the drugs were administered. Electroencephalograms were made with a six-channel Offner Type-A crystographic ink writer. The animals were free and unrestrained during the recording, connections to the electroencephalographic recorder being maintained by means of a light-weight cable and plug. The latter was introduced into the implanted socket on the head of the cat. The pH of all drugs tested was within the range of the diluent Tyrode solution, and the quantity injected at one time was never more than 0.2 cc. The cats were allowed to recover completely before new compounds were administered, unless specific antagonism experiments were in progress. The pH values of the cerebrospinal fluid and blood in an anesthetized cat (thiopental [Pentothal] sodium) were found to be 7.4 and 7.23, respectively.

Fig. 3.—Electrodes and plug.

RESULTS

Serotonin.—Doses of 75γ to 500γ (pH 7.6) were used on three different occasions, and they produced fairly consistent results. Within a few minutes after injection of serotonin, the pupils of the cat became mod-

Fig. 4.—Simulated injection into intraventricular catheter.

erately dilated transiently. The cat lay down quietly in a corner of the screened cage, alert and with the eyes open. Several times licking, and occasionally retching, was noticed. The cats cried when they were picked up. On two occasions a previously docile cat snarled and struck out at the observer. There was a tendency to maintain a fixed position, with the least spontaneous exploring or darting about. The animals walked in an unsteady manner and had muscular weakness. Although no classic catalepsy was seen, there was a tendency for the hindlegs to be stiff. Occasionally, there was a fine twitching of the head, with the mouth open. At times rhinorrhea appeared. Usually, the animals preferred the dark corner. There was no striking or consistent change in the respiratory rate. The electroencephalogram showed fast, low-voltage activity, consistent with an alert state.

Serotonin Followed by d-Lysergic Acid Diethylamide (LSD-25).—On three occasions, 24, 40, and 45 minutes after the intraventricular injection of serotonin, 15γ of LSD-25 (pH 7.4) was administered in the same manner. There were no striking changes in behavior or in the electroencephalogram. The reaction resembled the unopposed effect of serotonin, as noted in the controls.

LSD-25 Alone.—Restlessness and retching, which persisted intermittently throughout the period of observation, were early effects produced by the intraventricular injection of 15γ of LSD-25. Later, the cats became drowsy, and were less playful and less responsive to patting. There was no motor impairment in gait or jumping. The electroencephalogram revealed low-voltage, fast activity with occasional slow waves consistent with a relaxed state. There was no difference in the responses to hand clapping, kissing noises, or pinching, as compared with the control pattern.

LSD-25 Followed by Serotonin.—At various intervals within one hour after the administration of LSD-25, serotonin was injected intraventricularly in amounts of 250γ to 500γ without any evidence of a blocking effect of LSD-25. The effects of serotonin were the same as those described when serotonin was given alone.

Mescaline Alone.—Definite effects were observed after the intraventricular injection of mescaline in doses ranging from 0.3 to 15 mg. (pH 7.7). After the higher doses the cat started to cry and howl. There was a copious liquid bowel movement. The pupils were maximally dilated, and the animal had frequent paroxysms of scratching at the face and ears, sometimes using the two forelegs simultaneously. There were episodes of shaking the head and twitching of the right cheek, followed by passage of another loose stool. The cat was totally preoccupied with itching and became difficult to handle. With the onset of the howling and scratching, the electroencephalogram revealed 3 to 4 cps, sharp waves from all positions, maximal in the right temporal region. Without any clinical evidence of a motor seizure, there developed an 80-second paróxysm of 10 cps spikes, beginning in the right frontotemporal area and spreading to the occipital area, and finally to the whole left hemisphere. In the interparoxysmal period the electroencephalogram was characterized by a low-voltage, fast background and random 1 to 3 cps, sharp waves, maximal in the right hemisphere. This was followed by two other electroencephalographic paroxysms, lasting 70 and 50 seconds, respectively, and finally terminating in generalized, diffuse, high-voltage, slow waves and death. Necropsy revealed acute pulmonary edema, which probably was the cause of death.

Within five minutes after the injection of 1 mg. of mescaline into one cat, there occurred, every five seconds, complex paroxysms of sharp, positive deflection with many superimposed spikes, followed by a large, slow, negative phase in the right frontal area, with spread to the right temporal and occipital areas and the homologous areas on the left, except the left frontal area. Within 11 minutes these complex paroxysms became more frequent, and a 40-second episode of 14 cps spikes occurred in the right hemi-

sphere, with spread to the left occipital and temporal areas (Fig. 5). Over the 40-second interval this increased in voltage and slowed to 10 cps, and then finally ended abruptly, with restoration to the low-voltage, fast, control type of background. Additional complex paroxysms, leading to prolonged, diffuse spike activity, occurred. During neither of these episodes was there evidence of any motor convulsion. The cat could not be influenced by clapping, kissing noises, or whistling. The animal sat crouched and stared into space. When called or visually distracted, it would turn its head toward the source of stimulation. No behavioral

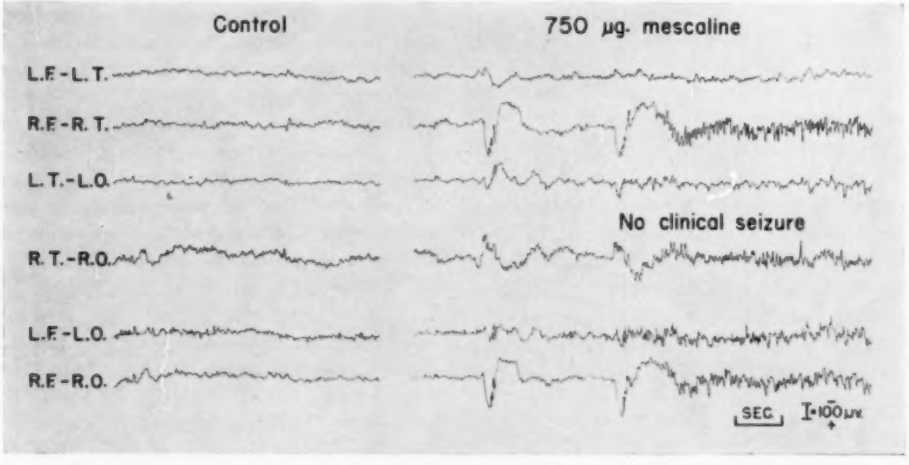


Fig. 5.—Electroencephalographic effect of intraventricular injection of 750γ of mescaline into a cat.

difference was noted either preceding or immediately following this spike episode. Even when the smaller doses were employed, the cats did not respond normally until six hours after the injection.

Mescaline Followed by Serotonin.—Seven, fifteen, and twenty-five minutes, respectively, after the injection of 1.0, 0.3, and 0.7 mg. of mescaline, each cat was given intraventricularly 500γ of serotonin (pH 7.6). In no instance was the progress of the effect of the mescaline halted. In the two instances in which the reaction was permitted to continue, the presumed effects of serotonin, such as increased licking, muscle relaxation, and retching, were observed. For several minutes there seemed to be an accentuation of muscular weakness. The electroencephalogram showed no essential changes other than the mescaline effects, which continued.

Adrenochrome.†—In doses ranging from 0.125 to 1 mg., a freshly prepared solution of pure adrenochrome (pH 7.7) administered intraventricularly produced states of drowsiness of various degrees. Within a few minutes the cats blinked, yawned, or retched. They then either sat or lay down and went to sleep. However, they were easily and readily aroused. They would sometimes suddenly look up toward the ceiling or around them and then remain motionless, staring into space. The gait was intact. After about 20 minutes the cats became moderately insensitive to painful stimulation. There was no prompt withdrawal or voicing of pain when the paw was squeezed or the ear was pinched. When cotton was hung over an eye, no attempt was made to shake it off. The cat generally withdrew on inhaling tincture

† A. Hoffer, M.D., Ph.D., Director of Psychiatric Research, Psychiatric Services Branch, Department of Public Health, Regina, Sask., Canada, supplied the pure adrenochrome and adrenolutin.

of valerian, and miauled. Yet the cats had a clear sensorium, insofar as they were affectionate and responded to petting with purring. They readily responded to a bowl of warm milk and shared it without quarreling. Their memory apparently was intact, because when they were left completely alone they would seek out one of their favorite resting places upon an instrument tray or bench. The cats could be placed on a chair and would remain sitting there for long periods, without jumping off and running away. After a short while the male cat mounted the small female cat and made frequent attempts to copulate. Although the observations are too few and the effects seemed to be a poorly balanced position. After the injection of 1 mg. of adrenochrome the cats were drowsy for 24 hours. The electroencephalographic changes accompanying these drowsy, trance-like states were occipital 4 cps, slow waves with low-voltage spike components, spreading to the frontal regions and then diffusely over the brain. There was inconstant electroencephalographic arousal when painful stimulation was employed. One cat with electrodes implanted over the auditory cortex showed a spike response to stimuli, such as hand claps, kissing sounds, and the sound of the metronome, similar to that observed in the control period. These single-response spikes were

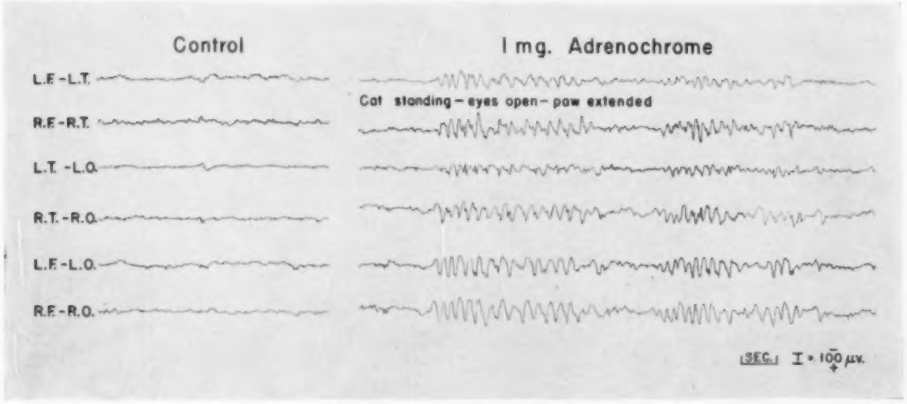


Fig. 6.—Electroencephalographic effect of intraventricular injection of 1 mg. of adrenochrome into a cat.

too inconstant to permit any conclusions, it must be noted that this behavior was not seen when any of the other drugs were used (except adrenolutin), nor did it appear spontaneously during the control periods. Although the female cat frequently would complain or cry out loudly when the nape of her neck was bitten too hard, she would always return to the male cat. Once a male cat attempted to copulate with a comatose dog, which was also in the laboratory. The cat frequently could hold its forelegs in a position behind its ears with minimal restraint before attempting to put them down. The male cat frequently rested his paw on top of the smaller female cat's head in what not related to the background electroencephalogram, which was unaltered unless the cat was clinically aroused. An arousal pattern appeared when the animal was drinking milk and when inhaling tincture of valerian. Many times the diffuse slow waves and spindles were noticeable when the cat was sitting up with the eyes open and expressionless (Fig. 6). During copulation the electroencephalogram described a background of low-voltage, fast activity. With cessation of the thrusts, there was a speedy reversion to the trance pattern.

Adrenochrome Followed by Serotonin and Nicotinic Acid.—In two instances, at 20 and 30 minutes after the administration of 200γ

and 500γ of adrenochrome, 250γ and 500γ of serotonin (pH 7.6) were injected. Aside from some initial retching and licking, the animals manifested no essential changes, either behaviorally or in the electroencephalogram, which continued to show the trance pattern unless the animal was aroused. After a few hours, however, both cats had copious, loose bowel movements. The intraventricular (1.25 mg. at a pH of 8.1) or intramuscular (25 mg.) administration of nicotinic acid did not have any influence on the effects of 1 mg. of adrenochrome.

Adrenolutin.‡—Four doses of a freshly prepared solution of adrenolutin (pH 7.6), ranging from 300γ to 650γ, were injected intraventricularly. The effects were similar to those produced by adrenochrome, except that they were more nearly immediate and pronounced. The cats became very drowsy and assumed unusual positions. Yet they were easily aroused. At times the cats suddenly made searching movements of the head, and then would lapse into a blank, staring expression. Although partially anesthetic, they would frequently lick and cry. The predominant frequency seen was in the theta range, with the occasional appearance of rhythmic, 3 cps discharges, resembling those produced when adrenochrome was used (Fig. 7). During copulation the electroencephalogram pattern was low-voltage, fast waves. In the doses used, the agent allowed the sensorium to remain clear, and the cats returned to their control status 24 hours later.

Ergotamine Tartrate.—On four separate occasions 20γ (pH 7.5) of ergotamine tartrate was injected intraventricularly. Within a few minutes frequent bouts of retching were noted. One of the cats vomited. Licking and hiccuping occurred. Both cats made feeble cries. They were still affectionate and playful. Although they seemed not to be so curious as before the experiment, they walked and jumped well. Despite the retching and miauling, the cats apparently were not in acute distress. They appeared to be relaxed and contented. The electroencephalogram showed a pattern characteristic of an alert state for most of the time, with infrequent episodes of high-voltage, 5 to 6 cps waves associated with apparent drowsiness. The cats could be alerted readily.

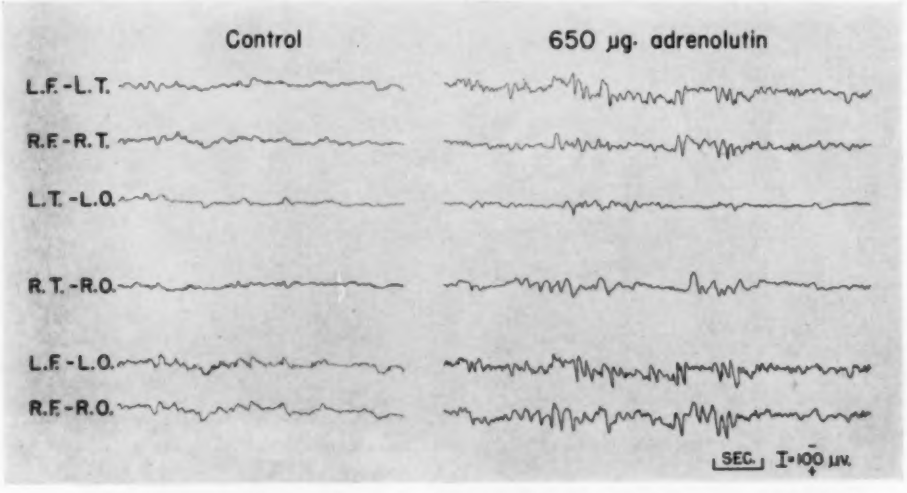


Fig. 7.—Electroencephalographic effect of intraventricular injection of 650γ of adrenolutin into a cat.

‡ Supplied by Dr. A. Hoffer, of Regina, Sask., Canada.

Ergotamine Tartrate Followed by Serotonin.—In all instances the behavioral reactions to the administration of ergotamine tartrate followed by serotonin resembled the response to serotonin alone, as described previously.

COMMENT

In general agreement with Feldberg and Sherwood's § experience with other drugs, the hallucinogenic drugs, when tested on the basis of behavior and electroencephalographic changes after direct intraventricular injection, show more similarities than differences. That the effects are truly central, and not peripherally mediated, is indicated in Feldberg's review of the literature and his own experiments with curarine and decamethonium. He found that convulsions and spastic paresis, respectively, were produced after intraventricular injection of the agents, instead of the flaccid motor paralysis that follows intravenous injection.

The behavioral changes ranged from fright and relative immobility (caused by serotonin) to stupor and anesthesia (caused by adrenochrome and adrenolutin) to the violent paroxysms of scratching that resulted from mescaline. Both LSD-25 and ergotamine tartrate produced similar effects in respect to pronounced retching followed by slight drowsiness. No antagonism was observed among any of the drugs used; namely, serotonin, LSD-25, mescaline, adrenochrome, adrenolutin, and ergotamine tartrate. The second compound injected seemed to exert its usual behavioral and electroencephalographic effect, and there was no suggestion of any protection conferred by the drug first injected. Stupor and catatonia, as described by de Jong,[5] were observed after the administration of adrenochrome and adrenolutin. After an initial gradual reduction in motor activity, the cats would finally sit in odd positions with their eyes wide open for long periods and howl. Although, for various reasons, the term "waxy flexibility" cannot be used as it would be used in referring to human beings, the cats permitted their limbs to be placed passively in unnatural positions without immediately correcting them, or even resisting such positions. In the presence of a clear sensorium, other bizarre forms of behavior were noted to follow the injection of adrenochrome and adrenolutin. Frequently, the cats were in a deep trance, with concomitant electroencephalographic changes; but they could always be alerted readily. The similarity of the effects of adrenochrome and adrenolutin to the reported actions of epinephrine and arterenol (norepinephrine) is striking.[1] The suggested relationship of an increased content of epinephrine and arterenol in the cerebrospinal fluid to the "exhaustion and fatigue" that follow strong emotional upheavals should hold equally well in the case of adrenochrome. Similar questions in reference to normal sleep and pathologic stupor also can be raised. Hoffer and associates[6] were the first to recognize the effects of adrenochrome on the central nervous system. The effects in question are (1) production of a model psychosis without insight in normal volunteer subjects, and (2) an increase in dysrhythmias in the electroencephalogram.[7] They speculated as to whether schizophrenia could be in part a disease of abnormal metabolism. Additional studies might reveal what areas of the ventricular system of the cat are susceptible, and what enzyme systems might be affected. Anatomically, the injected drugs could gain access to the autonomic areas that border the third ventricle or to many of the vital centers in the vicinity of the fourth ventricle.

The remarkable feature of LSD-25, when it is given intraventricularly, is the minimal effect which it exerts on the behavior of the cat. The dose used in the cat would be sufficient, if it were administered orally to some human beings, to cause a model psychosis. Presumably, comparable minimal doses of mescaline, on the other hand, caused a reaction of intense scratching and paroxysms of diffuse spike discharges in the electroencephalogram. Descriptively similar phenomena have followed the intraventricular injection of physostigmine, acetylcholine,

§ References 1 and 2.

and isoflurophate (diisopropyl fluorophosphate; DFP).‖

SUMMARY

Although the effects of some of the hallucinogenic drugs, when such drugs are administered by way of the blood stream of animals, are well recognized, the present study was particularly concerned with the intraventricular injection of some of these compounds. It should be noted that the effects of these agents may differ, according to which route of administration is employed.

By use of a polyethylene catheter permanently placed in the ventricles of the brain and six electrodes placed symmetrically in the frontal, temporal, and occipital regions, the behavioral and electroencephalographic changes in the trained cat were studied after the intraventricular injection of some hallucinogenic drugs and related compounds.

1. Serotonin produced muscular weakness, relative motor immobilization, and salivation, without any significant changes in the electroencephalogram.

2. LSD-25, or *d*-lysergic acid diethylamide, produced initially a restless state, with frequent bouts of retching. Later there was a tendency toward drowsiness, associated with occasional slow waves in the electroencephalogram.

3. No central nervous system, behavioral, or electroencephalographic antagonism was observed between serotonin and LSD-25 when these drugs were administered by the intraventricular route in the described doses.

4. Mescaline caused paroxysms of violent scratching. Later, but not necessarily associated with this scratching, electroencephalographic evidence of paroxysms of 10 cps spikes, occurring asymmetrically in the brain and spreading to homologous areas, was noted.

5. No antagonism between mescaline and serotonin was demonstrated when the intraventricular route of administration was employed.

6. Adrenochrome brought about a stuporous state, associated with electroencephalographic changes of 4 cps, slow waves, occurring in the occipital regions.

7. Adrenolutin (1-methyl-3,5,6-indolestriol), in smaller doses than adrenochrome, caused essentially similar behavioral changes, associated with rhythmic theta activity in the electroencephalogram.

8. Neither adrenochrome nor adrenolutin produced any evident antagonism when either was employed with serotonin via the intraventricular route.

9. Ergotamine tartrate when administered intraventricularly produced a condition of diminished spontaneous motor activity and episodes of vomiting and retching. The electroencephalographic changes were minimal and resembled those recorded when LSD-25 was administered.

10. No antagonism between ergotamine tartrate and serotonin was noted when these were administered intraventricularly.

REFERENCES

1. Feldberg, W., and Sherwood, S. L.: Injections of Drugs into the Lateral Ventricle of the Cat, J. Physiol. **123**:148-167 (Jan.) 1954.

2. Feldberg, W., and Sherwood, S. L.: Behavior of Cats After Intraventricular Injections of Eserine and DFP, J. Physiol. **125**:488-500 (Sept.) 1954.

3. Gaddum, J. H.: Antagonism Between Lysergic Acid Diethylamide and 5-Hydroxy-Tryptamine, J. Physiol. **121**:15P, 1953.

4. Woolley, D. W., and Shaw, E.: Some Neurophysiological Aspects of Serotonin, Brit. M. J. **2**: 122-126 (July 17) 1954.

5. de Jong, H. H.: Experimental Catatonia, a General Reaction-Form of Central Nervous System, and Its Implications for Human Pathology, Baltimore, The Williams & Wilkins Company, 1945.

6. Hoffer, A.; Osmond, H., and Smythies, J.: Schizophrenia: A New Approach: II. Result of a Year's Research, J. Ment. Sc. **100**:29-45 (Jan.) 1954.

7. Szatmari, A.; Hoffer, A., and Schneider, R.: The Effect of Adrenochrome and Niacin on the Electroencephalogram of Epileptics, Am. J. Pyschiat. **111**:603-616 (Feb.) 1955.

8. Cooke, P. M., and Sherwood, S. L.: The Effect of Introduction of Some Drugs into the Cerebral Ventricles on the Electrical Activity of the Brain of Cats, Electroencephalog. & Clin. Neurophysiol. **6**:425-431 (Aug.) 1954.

9. Royal Society of Medicine: Discussion on Intraventricular Administration of Drugs, Lancet **1**:900-901 (April 30) 1955.

‖ References 1, 2, 8, and 9.

Clinical Evaluation of Ambenonium (Mysuran) Chloride

MARTHA R. WESTERBERG, M.D., Ann Arbor, Mich.

This report is concerned with the results of the use of ambenonium in patients with myasthenia gravis during the past year. Ambenonium (Mysuran) chloride is N'N'-bis (2-diethylaminoethyl) oxamide bis-2-chlorobenzyl chloride, or C28H42C14N402. Its formula is

Pharmacologic investigation by Winthrop-Stearns, Inc., has shown that ambenonium chloride has anticholinesterase properties, which are specific against acetylcholinesterase, with only weak activity against serum cholinesterase, and that its activity is from 5 to 13 times that of neostigmine. In animal experiments, ambenonium was two to four times as active in antagonizing tubocurarine paralysis, and the effect was of much longer duration. The curarizing effect of ambenonium occurred only with doses approximately 1000 times the therapeutic level. Its acute toxicity in animals was one-tenth that of neostigmine, and its side-effects were characteristic of parasympathetic stimulation and were controlled by atropine.

The present study concerns the evaluation of the effect of ambenonium chloride in patients with myasthenia gravis. Ambenonium was available to us in a 10 mg. tablet and in a scored 25 mg. tablet, so that patients were able to take a 10, 12.5, or 25 mg. dose. Only oral ambenonium was used. Thirty-three patients took ambenonium for varying periods of time from August, 1954, to August, 1955. All were ambulatory outpatients who had previously used neostigmine, pyridostigmine (Mestinon) bromide, or tetraethyl pyrophosphate (TEPP). Twenty-five of the patients were female and 10 were male. Their ages ranged from 11 to 78 years, and the group, which was unselected, was fairly evenly divided in severity of their disease. Approximately one-third had mild myasthenia; one-third had moderate involvement, and one-third had moderately severe disease. One patient died during the course of the study.

Of the 33 patients, 26 found ambenonium to be an effective agent in increasing muscle strength, and 7 found it ineffective. Thirteen patients preferred ambenonium to any other anticholinesterase and continued to take it alone. Nine patients considered ambenonium equal to their other medication in its effect, and six of these continue to use it regularly. Twelve patients had unsatisfactory results with the medication.

REPORT OF CASES

Thirteen patients who felt that they were better on ambenonium than other therapy report as follows:

CASE 1.—A 66-year-old man with mild myasthenia had been taking 5 mg. of tetraethyl pyro-

Received for publication Oct. 28, 1955.

Ambenonium (Mysuran) chloride was furnished to us by Winthrop-Stearns, Inc., under the designation WIN 8077.

phosphate (TEPP) three times a day for many years. He found that 12.5 mg. of ambenonium chloride three or four times a day was a very satisfactory substitute for the long-acting TEPP, that his strength was as good or better, and that the ambenonium was easier to use. He takes atropine about once a day with the ambenonium, which he has used for one year.

CASE 2.—A 17-year-old girl with moderately severe myasthenia has varied in her dosage over a 10-month period, using from 90 to 300 mg. of ambenonium chloride daily in place of 720 to 1200 mg. of pyridostigmine bromide. She substituted 18 tablets of pyridostigmine for 8 of the 25-mg. ambenonium tablets for two weeks and reported that she was weaker while taking the pyridostigmine. She had abominal pain only with an overdosage with ambenonium.

CASE 3.—A 21-year-old woman with moderately severe myasthenia finds 110 mg. of ambenonium chloride a day as effective as 15 to 20 tablets of pyridostigmine bromide or 40 to 50 tablets of neostigmine bromide. She has no side-effects from the present dosage.

CASE 4.—A 46-year-old man with mild myasthenia found 50 to 75 mg. of ambenonium chloride a day preferable to combined TEPP and pyridostigmine and was able to discontinue the use of TEPP. He has had no side-effects.

CASE 5.—A 53-year-old woman with moderately severe myasthenia has greater strength on 80 to 100 mg. of ambenonium chloride daily than with 960 mg. of pyridostigmine bromide and has experienced no ill effects and requires no atropine.

CASE 6.—A 43-year-old man with mild myasthenia takes 45 mg. of ambenonium chloride daily as a substitute for 9 mg. of TEPP and feels stronger than before. He requires atropine to cover gastrointestinal symptoms.

CASE 7.—A 65-year-old woman with a mild degree of myasthenia finds 60 mg. of ambenonium chloride more effective than 240 mg. of pyridostigmine bromide and has experienced no side-effects other than "dizziness" with doses of 200-300 mg. per day.

CASE 8.—An 11-year-old girl with rather severe myasthenia now takes 150 to 200 mg. of ambenonium a day, in place of a combination of 180 mg. of pyridostigmine bromide and 45 mg. of neostigmine. She is the only patient who takes more medication than she had previously used, but has no side-effects whatsoever and has been gaining weight.

CASE 9.—A 53-year-old housewife with moderate myasthenia gravis reports that 50-75 mg. of ambenonium chloride is equivalent to 800-900 mg. of pyridostigmine bromide and stronger than 600 to 1200 mg. of neostigmine. She has dizziness, cramps, and diarrhea with overdosage of ambenonium, but none with her present maintenance dose.

CASE 10.—A 37-year-old woman with severe myasthenia died suddenly and unexpectedly at home while taking ambenonium chloride, 100 mg. daily, a combination supplemented by two or three tablets of pyridostigmine or neostigmine (Prostigmin), which she had taken without variation for three months. She did not use atropine and liked the ambenonium because of its quick action and overnight effect.

CASE 11.—A 19-year-old college girl with moderately severe myasthenia had taken a daily dose of 900 mg. of pyridostigmine bromide regularly, when she was given ambenonium to try. For 10 months she has taken 75 mg., and occasionally 100 mg., of the latter in its place. She reports no side-effects, but is much stronger and has gained weight. She had previously used 315 mg. of neostigmine per day.

CASE 12.—A 44-year-old man who has myasthenia of moderate degree had originally taken 360 mg. of neostigmine bromide, which was replaced by 720 mg. of pyridostigmine bromide a day. He reports that 75 mg. of ambenonium each day makes him stronger than either of the previous medications, and "with less ill effect than either of my other medicines."

CASE 13.—A 31-year-old housewife finds 25 to 50 mg. of ambenonium chloride equal to 360 to 480 mg. of pyridostigmine bromide, but her course is so variable that exact comparison is difficult.

Twelve patients reported poor results with ambenonium, as follows:

CASE 1.—A 27-year-old housewife with mild myasthenia, who was taking 540 mg. of pyridostigmine bromide, took 75 to 100 mg. of ambenonium chloride a day with good strength; but on the third day she developed headache and dizziness, her "eyes were jumpy and could not focus," and she felt "drugged" and confused. She also complained of periorbital, facial, and faucial swelling. It was believed that this might be an allergic, as well as a toxic, effect of the drug, but she has since taken 10 mg. each day as a supplementary dose in the morning with no ill effect.

CASE 2.—A 29-year-old woman with severe myasthenia, who was taking TEPP and pyridostigmine, reports of her trial of ambenonium: "I just don't get any strength from it." With overdosage the patient was mildly dizzy, nauseated, and shaky but had no severe reactions.

CASE 3.—A 42-year-old school teacher reported that 25 mg. of ambenonium chloride three times daily made her feel "shaky, jittery, and overstimulated, preventing sleep," but she is currently taking

pyridostigmine, neostigmine, and 10 mg. of ambenonium chloride ad lib., stating that if she could have just one drug she would prefer pyridostigmine. She reported no cramps or diarrhea with ambenonium.

CASE 4.—A 23-year-old woman with severe myasthenia discontinued ambenonium after a three-day trial because of insufficient strength, and it was not considered wise to continue use of the drug. She reported abdominal cramps with a 25 mg. tablet.

CASE 5.—A 47-year-old housewife with mild myasthenia, who is extremely sensitive to neostigmine, had a similar severe reaction to both 25 and 10 mg. of ambenonium chloride. Her toxic reaction included drooling, abdominal cramps, sweating, generalized twitching, and incapacitation. She reverted to the use of pyridostigmine.

CASE 6.—A 19-year-old woman with severe myasthenia who was maintained on 15-18 tablets of pyridostigmine bromide, in addition to 15 mg. of TEPP each day, took up to 16 tablets (400 mg.) of ambenonium daily during a four-day trial period without obtaining sufficient strength and discontinued the medication. She had no undesirable side-effects.

CASE 7.—A 75-year-old woman with moderately severe myasthenia had an unsupervised trial of ambenonium while out of the country. She reported inadequate strength, cramps, and diarrhea and stopped taking it after one week.

CASE 8.—A 45-year-old housewife at first preferred ambenonium because it "worked faster and lasted longer" than pyridostigmine but took increasingly large amounts, up to 15 tablets (375 mg.) a day, although she has mild to moderate myasthenia, and with overdosage became "stiff, weak, and dizzy" and suffered headache.

CASE 9.—A 47-year-old housewife with moderate myasthenia found her strength inadequate on 43 mg. per day. With 75 mg. of ambenonium chloride daily her strength was good, but she had headache and discontinued the drug after 10 days.

CASE 10.—A 26-year-old woman with rather severe myasthenia discontinued ambenonium after a month's trial because she had "too many ups and downs, like Prostigmin," although her strength was better at peak than it was with pyridostigmine and she stated that the drug took effect within 20 minutes. She used 250 mg. of ambenonium chloride in place of 1020 mg. of pyridostigmine bromide daily.

CASE 11.—A 38-year-old nurse with mild myasthenia gravis was taking 180 mg. of pyridostigmine regularly each day when asked to substitute ambenonium. She reported that 80 mg. of ambenonium chloride each day left her weaker than she had been for two years, and when she increased the dose to 100 mg. daily, her "stomach felt torn up."

CASE 12.—An 18-year-old woman with mild myasthenia reported that she tried 20 mg. of ambenonium each night in place of pyridostigmine, but discontinued it after a few days because she found she was much weaker in the morning on this program than while taking 60 mg. of pyridostigmine each night.

COMMENT

It has been shown that ambenonium is an effective drug in the treatment of myasthenia gravis,[1] and that for some patients it is the most effective drug available. The requirement of ambenonium seems to be approximately one-fifth to one-tenth that of neostigmine and, on the average, one-eighth that of pyridostigmine, milligram for milligram. Most patients compared the drug in this study with pyridostigmine, rather than with neostigmine, and found that one 25 mg. tablet of ambenonium chloride was equivalent to about 3 or 4 tablets of pyridostigmine. Few patients needed more than 3 or 4 tablets of ambenonium a day. This difference in dosage appears to be due, at least in part, to the longer duration of action of ambenonium. Many patients stated that they no longer needed to take medication before breakfast if they took ambenonium at bedtime. Many others found it possible to substitute ambenonium for tetraethyl pyrophosphate because of this prolonged action.

Most patients take pyridostigmine "by the clock" because of its slow onset of action; they cannot afford to let themselves run down because it takes too long for the next dose to pick them up again. Ambenonium, on the other hand, resembles neostigmine more closely in the rapid onset of its effect and should be taken as weakness appears, rather than prophylactically, at least until an appropriate schedule is worked out.

Ambenonium is less toxic than neostigmine but is more toxic than pyridostigmine as far as undesirable side-effects are concerned. The toxic effects are both those of a muscarinic nature and those of central nervous system stimulation. This factor of unfamiliar toxicity, together with the much stronger and longer action of the ambenonium, made it difficult at times to adjust the dosage, since

almost all patients tended to take too much medication, and several of the poor results necessitating discontinuance of ambenonium were due to simple overdosage rather than to failure of response to the drug. Gastrointestinal symptoms did not appear early, nor were they prominent in their appearance; and it was found that headache and vertigo with nystagmus were more reliable indications of toxicity. Difficulty with visual focus, complained of by some patients, may have been due either to nystagmus or to the curarizing effect upon extraocular muscles. The experimental finding of a very high ratio between curarizing and therapeutic doses seems to be borne out, in part at least, by a patient who took as much as 1200 mg. of ambenonium in one day and was still ambulatory and had no gastrointestinal symptoms. Another patient took 625 mg. of the drug in one day without becoming incapacitated. The tolerance dose for these two patients far exceeded their maximum effective dose and illustrates both the difficulty in determining the optimum dosage and the relative safety of the drug.

CONCLUSION

Ambenonium (Mysuran) chloride is effective in the treatment of myasthenia gravis.

Its potency and duration of action are greater than those of either pyridostigmine or neostigmine.

The toxic effects of ambenonium, which are less than those of neostigmine and greater than those of pyridostigmine, consist of both parasympathetic overactivity and central nervous system stimulation.

Caution should be exercised in using the drug and the low-dosage requirements stressed when converting patients accustomed to taking other anticholinesterase agents.

REFERENCE

1. Schwab, R. S.; Marshall, C. K., and Timberlake, W.: Win 8077 in Treatment of Myasthenia Gravis, J. A. M. A. **158**:625 (June 25) 1955.

News and Comment

GENERAL NEWS

New York State Psychiatric Institute Exhibit.—The New York State Psychiatric Institute, 722 W. 168th St., New York, will exhibit a portion of the material held in the Freud Memorial Room of its Library. This exhibition will open on Jan. 16, 1956, and continue through Feb. 10, 1956. This is the first of such exhibitions which will be held by various institutions during 1956, the centenary of the birth of Sigmund Freud.

The exhibition will include copies of the early neurological publications of Freud, copies of the first publications in the field of psychoanalysis, several holograph manuscripts by Freud, several of Freud's books with their translations into 14 different languages, books inscribed by Freud and books inscribed to Freud, letters written by Freud, documents signed by Freud which relate to the Viennese Psychoanalytic Society, and a collection of photographs of Freud. All of the material to be exhibited is the property of the Library of the Psychiatric Institute, which holds a considerable part of Freud's original library.

Studies in Pharmacological Psychotherapy

I. Treatment of Refractory Psychoneuroses and Personality Disorders with Thiopental (Pentothal) Sodium and Methamphetamine (Desoxyn)

THEODORE ROTHMAN, M.D.
and
KEITH SWARD, Ph.D., Beverly Hills, Calif.

This paper concerns the use of pharmacological psychotherapy with 16 moderately to severely disturbed patients, all of whom had previously undergone psychoanalysis over periods ranging from six months to three years. All these prior efforts at therapy had involved professionally qualified psychoanalysts; all had terminated unsuccessfully.

FAILURE OF PSYCHOANALYSIS

As a point of departure, we tried to determine what these patients believed to be the causes of their earlier failure to respond favorably to psychoanalysis. The feelings on this score were somewhat uniform. Commenting on their unsuccessful psychoanalyses, these patients reported, with varying emphasis from person to person, (1) an inability to communicate effectively, (2) an impersonal attitude on the part of the psychoanalyst, (3) difficulties in relating to the psychoanalyst, (4) failure to experience meaningful emotional reactions during the therapeutic hour, (5) mounting anxiety as treatment progressed, and (6) exacerbation of symptoms after an initial period of slight relief.

Received for publication Aug. 2, 1955.

A generous supply of the Desoxyn used in this study was provided by the Abbott Laboratories, North Chicago, Ill.

Read before the Section on Psychiatry and Neurology at the 84th Annual Meeting of the California Medical Association, San Francisco, May 4, 1955.

FAILURE OF PSYCHOTHERAPY

When the 16 previously psychoanalyzed patients began psychotherapy with us, the outlook was not favorable. Both patient and therapist in each case sensed the same complications that had doomed the earlier efforts at therapy. Once again, over a trial period of from one to three months of treatment, these patients experienced (1) an inability to form a close interpersonal relationship without disabling anxiety, (2) rising psychic tension, and (3) resultant difficulties in meaningful communication. A second therapeutic failure appeared imminent.

THE CASES

The prospect of another impasse in therapy was all the more likely in view of the psychopathology and the degree of incapacitation involved. All the patients in the group had rigid personality structures and thought of themselves as lifelong failures. All had severe disturbances of adaptation on every level of experience—occupational, social, and intrapsychic.

Of the 16 cases under consideration, the psychiatric diagnoses revealed nine personality trait disorders of the passive-aggressive type, one personality pattern disorder of the schizoid character, and six psychoneuroses, four of which were obsessive-compulsive reactions and two anxiety states.

As an index of the degree of impairment at the point of original consultation, we followed the schema prepared by the Committee on Nomenclature and Statistics of the American Psychiatric Association.[1] We used the patient's occupational and social adaptation as a base line for our estimates of disability—the degrees of difference ranging from "no

TABLE 1.—*Character and Duration of Previous Experience with Psychoanalysis*

Cases	Disorders *	Degree of Impairment †	Length of Psychoanalysis	School of Psychoanalysis ‡
1	Obsessive-compulsive reaction	+++	2½ yr.	Freudian, M.D., 2 yr. Jungian, M.D., 6 mo.
2	Obsessive-compulsive reaction	++++	2 yr.	Freudian, M.D.
3	Obsessive-compulsive reaction	++++	4 yr.	Freudian, M.D., 1 yr. Adlerian, M.D., 3 yr.
4	Passive-aggressive personality	+++	7 mo.	Freudian, M.D.
5	Passive-aggressive personality	++++	2 yr.	Adlerian, M.D.
6	Passive-aggressive personality	++++	2 yr.	Adlerian, M.D.
7	Passive-aggressive personality	+++	1 yr.	Adlerian, M.D.
8	Passive-aggressive personality	+++	1 yr.	Adlerian, M.D.
9	Passive-aggressive personality	+++	7 mo.	Freudian, M.D.
10	Passive-aggressive personality	++++	3 yr.	Freudian, M.D.
11	Passive-aggressive personality	+++	2 yr.	Freudian, PH.D.
12	Passive-aggressive personality	+++	6 mo.	Freudian, M.D.
13	Anxiety reaction	+++	3 yr.	Adlerian, M.D.
14	Anxiety reaction	+++	2 yr.	Freudian, M.D.
15	Schizoid personality	++++	3 yr.	Freudian, PH.D.
16	Phobias, obsessive-compulsive reaction	+++	1 yr.	Freudian, M.D., 6 mo. Adlerian, M.D., 6 mo.

* For nomenclature see "Diagnostic and Statistical Manual: Mental Disorders." [1]

† Degree of impairment based on estimate of patient's occupational and social adjustment.

Degree of Disability	Insignia
Minimal (10%)	+
Mild (20%-30%)	++
Moderate (30%-50%)	+++
Severe (50% or more)	++++

‡ Qualified psychoanalysts recognized by their respective professional societies (i. e., American Psychoanalytic Association, American Society of Adlerian Psychology, or Society of Analytical Psychology).

impairment"; "minimal impairment," not to exceed 10% disability; "mild impairment," 20% to 30% disability; "moderate impairment," 30% to 50% disability, to "severe impairment," over 50% disability. While we are aware of the subjective nature of this approach, we felt it necessary to adhere to some accepted criterion.

From an examination of Table 1, it will be seen that all of our subjects had either moderate or severe impairment at the time we first saw them. It will be noted, further, that the 16 patients had been psychoanalyzed over intervals extending from six months to three years and that the therapists in question were for the most part qualified psychoanalysts, that is, members of the American Psychoanalytic Association, the American Society of Adlerian Psychology, or the Society of Analytical Psychology.

We call attention to the high incidence of obsessive-compulsive traits throughout this series of 16 cases (Fig. 1). There are, to begin with, the four cases in which the

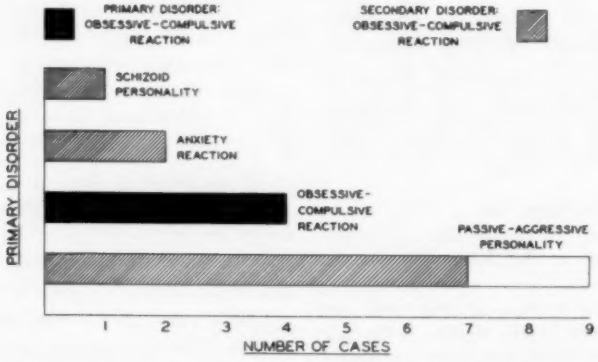


Fig. 1.—Incidence of obsessive-compulsive state as the primary or secondary disorder.

obsessive-compulsive reaction constituted the primary disorder. In 10 of the remaining 12 cases, which fell in different categories, the obsessive-compulsive reaction was present as a related or an associated state. That is, in these 10 cases, obsessive-compulsive components were so conspicuous that we frequently found it difficult to decide whether the obsessive-compusive element was primary or secondary in character.

PRINCIPLES OF PHARMACOLOGICAL PSYCHOTHERAPY

In an effort to overcome the inaccessibility of this group of patients, whose difficulties were obviously rigid and chronic in character, we sought to produce an optimum psychophysiological state for psychotherapy with the aid of pharmacological agents. We first tried working with intravenous thiopental (Pentothal) sodium alone. The immediate effect which we noted in our patients did not differ basically from comparable reports recorded 25 years ago by the pioneers in this field (Horsley,[2] Lindemann,* and Bleckwenn † or from the more recent observations of Grinker,[7] Hoch,‡ Sargant,§ and Grinker and Spiegel[16]; i. e., the thiobarbiturates given intravenously are, without question, anxiety-reducing. While under the influence of the drug, our uncommunicative patients became more or less unguarded, receptive, friendly, and expansive; they were more inclined to reveal hidden motivation.

We soon noted, however, that working with anything but small amounts of thiopental sodium tended to hinder, rather than enhance, the psychotherapeutic experience. Both the doses and the methods of administration generally reported in the literature ‖ left patients in a dazed and narcotized state; these coarse techniques produced artifacts of sedation, such as excessive abreactions and an amnesia for the interview. At this point we began to appreciate how the procedure of narcoanalysis or narcosynthesis had acquired its name and why many of the past and current efforts at pharmacological psychotherapy have ended in failure. Most of the earlier investigators in this area, influenced perhaps by the tradition or example of hypnosis, had, unfortunately, concentrated on the concept of sleep or narcosis.

These observations prompted us to experiment with progressively smaller doses of thiopental sodium. We began working with the drug in amounts small enough to permit adequate contact and full recall, yet large enough to reduce the operation of the patient's hypervigilance. Our search for the effective minimal dosage was aided by an electroencephalographic study of 10 apparently normal subjects.¶ These observations revealed that the doses generally reported in the literature produced high-voltage fast waves, interspersed with spindles and high-voltage slow waves, and a corresponding clouding of consciousness. We concluded that the minimum effective doses, for the purpose of facilitating psychotherapy, ranged from 3 to 7 cc. of 2.5% thiopental sodium administered intravenously at a rapid rate. An intravenous injection of 5 cc. sufficed for most patients.

Still another psychotherapeutic obstacle presented itself, even with the use of these minimum amounts of thiopental sodium. However small the dose, it was our experience that all patients on occasion seemed to remain somewhat somnolent and apathetic or were inclined to have a partial amnesia for the therapeutic experience.

Meanwhile, we had been following with interest the experimental work on cortical stimulants, such as *d*-desoxyephedrine (Pervitin) and methamphetamine.# Our own research led us to feel that the ampheta-

* References 3 and 4.

† References 5 and 6.

‡ References 8 to 13.

§ References 14 and 15.

‖ Bleckwenn.[6] Gottlieb.[17] Grinker.[7] Horsley.[2] Keane and Kant.[18] One of the traditional methods of administering one or another of the thiobarbiturates is to inject the drug until a patient's speech becomes slurred.

¶ We shall report these findings in detail at a later time.

Hoch, Cattell, and Pennes.[11] Levine, Rinkel, and Greenblatt.[19] Simon and Taube.[20] Straker.[21]

mine-like drugs, especially when used alone, should be administered with great caution in order to forestall the possibility of touching off abreactions of so excessive a quantity or of so intense and explosive a nature that neither patient nor therapist is capable of handling them.* It was our further impression that the amphetamine-like drugs tend to induce marked discomfort in certain patients through toxic side-effects, i. e., insomnia, headache, palpitations, nausea, and loss of appetite. Such complications had to be avoided, we felt, lest patients react with anxiety to the whole therapeutic situation.

We decided, finally, to explore the synergistic effect of using one of the drugs in the amphetamine series in combination with an antagonist. It was our hope that a suitable antagonist would react with the amphetamine-like drug by neutralizing the adverse side-effects, without reducing the stimulating properties, of the latter. We seemed to achieve the desired effect by using thiopental sodium followed by methamphetamine, administered intravenously.†

In summary, the apparent effect of this sequence of drugs, when administered to the patients on whom we are reporting, was to decrease psychic tension and hypervigilance, to induce a state of alertness, to promote feelings of spontaneity and well-being, to enhance rapport and interpersonal communication, to increase drive and responsiveness in all channels of communication, and to diminish autonomic nervous system overflow, thus reducing the patient's previous insulation to psychotherapy. In our opinion, our 16 refractory patients were now, for the first time, available for effective psychotherapy.

* Such were the effects described by Hargrove, Bennett, and Steele [22] in their investigation of carbon dioxide as an adjunct to psychotherapy.

† Abraham Myerson (References 23, 24, and 25) was apparently the first investigator to report the reciprocal action of two comparable drugs—amobarbital (Amytal) sodium and amphetamine (Benzedrine). Other investigators have subsequently confirmed Myerson's observations (Gottlieb and Coburn [17]; Keane and Kant [18]; Sargant and Slater [15]; Simon and Taube [20]).

TECHNIQUE OF PHARMACOLOGICAL PSYCHOTHERAPY

Preparation.—Before initiating the procedure of pharmacological psychotherapy in any case, we felt it necessary to observe several conditions: (1) to ascertain that there were no physical contraindications to the use of either thiopental sodium or methamphetamine,‡ (2) to be sure of a reasonably good preexisting psychotherapeutic relationship, and (3) to prepare the patient psychologically for his forthcoming experience with this method of treatment.

By way of preliminary explanation, we found it imperative to make clear that the medication we were about to use would not be sleep-inducing, that the patient would remain awake and in complete control of all his faculties throughout any of the succeeding interviews, and that he could anticipate some immediate reduction of anxiety and psychic tension both during the therapeutic hour and for a variable period following the treatment hour. The probable long-term effect of the new procedure we interpreted in advance as that of shortening the treatment process in some degree, of making psychotherapy more effective because of readier communication, and of relaxing the patient so that he could more easily discuss the life experiences and the hidden motivations that had prompted him to seek psychotherapy in the first place.

It was our experience that this psychotherapeutic technique was contraindicated for any patient who continued to show a persistently marked fear of the procedure. Going ahead with the technique in the face of the above resistance, we felt, ran the risk of inducing undesirable abreactions or of having the patient feel that he was in some fashion under attack by an authoritarian figure. Adverse reactions of such a character have been a very rare occurrence to date with any of the patients we have treated with this procedure.

Method of Administration. — The technique which we developed for administering

‡ References 26 to 31.

the drugs in question was as follows: First, a freshly prepared 2.5% solution of thiopental sodium was injected intravenously through a 10 cc. syringe. For the great majority of our cases, 3 to 7 cc. of the drug, rapidly injected, produced the desired effect. Such an injection had as its immediate reaction a loss of consciousness or a dazed state lasting from 30 seconds to 2 minutes, as well as an abrupt stoppage of respiration, persisting from 5 to 20 seconds, gradually followed by slow, shallow, and occasionally stertorous respirations. Then, into the same needle 5 to 15 mg. of methamphetamine hydrochloride was injected rapidly from a 2 cc. syringe.

The main object of the initial administrations, we felt, was to determine the tolerance to both the thiopental sodium and the methamphetamine. We then adjusted the relative proportion of the two drugs, given in sequence, until we arrived at the minimum effective dose for any given patient.

Frequency of Treatment.—The patients in this series had 50-minute interviews, occurring, on the average, once or twice weekly. Immediately following the shift to pharmacological therapy, therapeutic hours free of drugs were only occasionally interspersed with "drug interviews." As patients improved, however, we moved toward the goal of using an increasing proportion of drugless interviews, until at the point of termination the pharmacological aids could be dispensed with entirely.

Psychotherapy.—Once we had induced the optimal psychophysiological state, the psychodynamic processes which one associates with successful psychotherapy came into play.§ These growth processes,‖ which previous therapy had failed to release, included, in varying degrees, (1) lowering of the ego defenses; (2) enhanced communication at an emotional level; (3) increased tolerance for facing unconscious motivations; (4) more active patient participation in the therapeutic experience¶; (5) a healthy, evolving rapport between patient and therapist; (6) magnification and easier management of "transference" reactions; (7) an increase in the patient's capacity for integration; (8) enhanced self-esteem on the part of the patient; (9) reinforcement of the "drive toward health"; (10) greater capacity on the part of the patient for "breaking through" his psychic paralysis, and (11) creation of an optimal learning situation.

Needless to say, this technique in its entirety is no worker of miracles. It is a form of slow, intensive psychotherapy. It effects, when successful, a gradual amelioration of a patient's state of suffering and maladaptation. It taxes the skills of the therapist to the utmost. An incompetent or inexperienced psychotherapist who employed this method of treatment would be prone to release frequent and unmanageable abreactions. He would also find his usual therapeutic errors magnified. Thus, instead of alleviating symptoms, he would be aggravating them.

RESULTS OF TREATMENT

As a frame of reference for evaluating our results, we again made use of the "categories of impairment" proposed by the Committee on Nomenclature and Statistics of the American Psychiatric Association.[1] That is, improvement, as we define it subjectively, consists of a patient's shift from one level of disability to a less serious level of disability. For example, if a patient appeared to move on the four-step scale of incapacitation from a state of "moderate impairment" (30% to 50% disability) to a state of "mild impairment" (20% to 30% disability), we classified this single degree of change as one represent-

§ References 32 to 37.

‖ In this paper we can only label or enumerate these growth processes. At a later time, we shall attempt to spell out in detail the psychotherapeutic procedure and the underlying psychodynamics which we feel are involved in pharmacological psychotherapy.

¶ This observation is at variance with the oft-repeated impression that pharmacological psychotherapy plunges a patient into a passive-dependent, regressive, or helpless child-like state. Such a criticism, to be sure, has been leveled not at the type of experience we are reporting but at something entirely different—"narco-analysis" or "narco-synthesis."

ing "slight improvement." Two degrees of change in the direction of amelioration we categorized as showing "moderate improvement," and so on.

The majority of our cases showed slight to considerable improvement; i. e., they moved from one category of impairment to categories of less severe impairment. Once more, in Figure 2, we call attention to the fact that, before the initiation of pharmacological psychotherapy, all 16 of our patients were suffering from moderate to severe disabilities. At the point of intake, 10 of our cases showed "moderate impairment" (30% to 50% disability), and 6 showed "severe impairment" (50% or more disability).

More specifically, 43.7% of our admittedly small sample of refractory cases improved to a slight degree; they moved from one level of impairment to the next less serious level of impairment (Table 2). Nearly one-third of the total group (31.3%) showed a moderate degree of amelioration, moving from a given category of incapacitation to a less serious category of incapacitation two steps removed. Slightly more than 6% of the sample (6.3%) registered considerable improvement. Roughly one-fifth (18.7%) of our cases, after one to two years of treatment, made no progress whatsoever.

TABLE 2.—*Summary of Changes Following Pharmacological Psychotherapy*

Degrees of Improvement	Cases	
	No.	%
None (0)	3	18.7
Slight (1+)	7	43.7
Moderate (2+)	5	31.3
Considerable (3+)	1	6.3
Totals	16	100.0

Taken at their face value, our results are statistically significant. Again, 13 of our 16 cases showed improvement; 3 showed no discernible change; none showed a change in a "negative" direction. The so-called sign test reveals that these findings lie far beyond chance.#

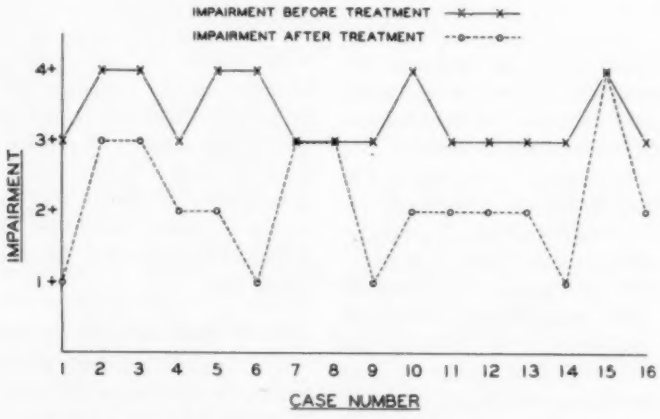


Fig. 2.—Results of treatment with pharmacological psychotherapy.

In applying the sign test to a situation where the possibilities include "positive change," "negative change," and "no change," it is customary to treat the "no-change" cases as ties. The test is then based upon the distribution of the remaining cases, which would be represented in this instance by 13 cases showing improvement, with no changes in a negative direction. When our results are subjected to the sign test in this manner, the difference in favor of "improvement" is significant at the 0.0001 level [$(\frac{1}{2})^{13} = 0.0001$]. Some investigators may prefer to classify the three "no-change" cases as negative instance. Even with this more stringent criterion, the difference in favor of "improvement" is significant at the 0.05 level of confidence. These statements of probability rest, of course, on the assumption that our underlying clinical observations represent "good" data. Dixon and Massey.[38] Fischer.[39]

TABLE 3.—*Results of Treatment with Pharmacological Psychotherapy*

Cases	Disorders	Length of Treatment	Extent of Impairment: Before Treatment	Extent of Impairment: After Treatment	Degrees of Change
1	Obsessive-compulsive reaction	3 yr.	+++	+	2+
2	Obsessive-compulsive reaction	6 mo.	++++	+++	1+
3	Obsessive-compulsive reaction	4 yr.	++++	+++	1+
4	Passive-aggressive personality	1 yr., 3 mo.	+++	++	1+
5	Passive-aggressive personality	2 yr.	++++	++	2+
6	Passive-aggressive personality	2 yr.	++++	+	3+
7	Passive-aggressive personality	1 yr.	+++	+++	0
8	Passive-aggressive personality	2 yr.	+++	+++	0
9	Passive-aggressive personality	1 yr., 3 mo.	+++	+	2+
10	Passive-aggressive personality	1 yr., 4 mo.	++++	++	2+
11	Passive-aggressive personality	2 yr., 6 mo.	+++	++	1+
12	Passive-aggressive personality	7 mo.	+++	++	1+
13	Anxiety reaction	4 yr.	+++	++	1+
14	Anxiety reaction	6 mo.	+++	+	2+
15	Schizoid personality	2 yr.	++++	++++	0
16	Phobias, obsessive-compulsive reaction	7 mo.	+++	++	1+

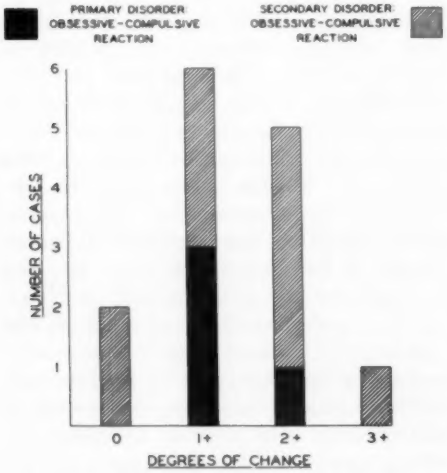


Fig. 3.—Results of pharmacological psychotherapy in 14 cases with obsessive-compulsive reaction as the primary or secondary disorder.

In Table 3, which summarizes our results in more detail, it can be seen that our treatment situations were prolonged in character. The length of care extended from six months to four years, with a median treatment time of one year and eight months. It follows, again, that with chronic and moderate to severe disorders of the sort we are discussing, pharmacological psychotherapy is by no means to be equated with brief psychotherapy.

The surprising feature of our results lies in the fact that improvement seemed to occur in a series of patients whose personality difficulties included so large an admixture of moderate to severe obsessive-compulsive states, as either the primary or the secondary disorder (Fig. 3).

This degree of amelioration, however partial or undramatic, is suggestive and provocative. It departs from the all but universal report of earlier investigators to the effect that the prognosis with pharmacological psychotherapy is highly unfavorable for patients who are suffering from serious obsessive-compulsive states of long standing. At the same time, we would be the first to acknowledge that with chronic obsessive-compulsive reactions of the severest degree the prognosis is poor, irrespective of the mode of therapy employed.

COMMENT

This study is frankly exploratory in character. Its method is one of clinical observation. Its primary object is that of formulating both a technique and a conceptual framework that can be checked by other investigators. Certainly, future studies in the same area must be more rigidly designed; they must use adequate control groups and employ more complete and more reliable measures

of change. Fuller and more controlled observations of this character have recently been reported by the Anesthesia Laboratory of the Harvard Medical School and by Nowlis and his co-workers, at the University of Rochester.*

Our aim, again, was to find an optimal psychophysiological state that would enable a group of refractory patients to benefit from a psychotherapeutic situation. The technique we have reported seems to induce a condition of altered permeability, thereby reversing what appear to be irreversible disorders. This change with the previously inaccessible patient we would explain, psychodynamically, somewhat as follows: (1) During the therapeutic hour, and for a variable interval thereafter, the patient is cushioned against the crippling effect of severe anxiety; (2) at the same time he experiences a marked increase in drive, mental alertness, and goal-oriented behavior; (3) he becomes, accordingly, less blocked and constricted and better able to function as a participant observer in detecting and reappraising his security operations and the associated anxiety that has shaped and perpetuated these sundry defensive measures; (4) the patient also finds himself able to communicate on a feeling level with less guilt and panic, no longer so immobilized by the dread of self-exposure or the fear of possible disintegration; (5) finally, to paraphrase David Riock, pharmacological psychotherapy enables the seemingly intractable patient — the "excommunicated one"—to enter into a two-person relationship in which he can experience, often for the first time in his life, stable, continuing communication, thanks to the benign interaction with another human being.†

The technique we are describing must be sharply distinguished from the procedures variously known as "narcoanalysis," "narcotherapy," or "narcosynthesis." Our method of approach differs from the latter in both its pharmacology and its psychodynamics. "Narcoanalysis," by definition, employs no cortical stimulants. Its reliance, for the most part, on sedative doses of one or another of the thiobarbiturates has led into a dead end and has run afoul of all the complications which we recounted earlier in this paper. There seems to be a definite minimal dosage of medication for producing the optimum psychophysiological state for psychotherapy. On a psychodynamic level, most of the advocates of "narcotherapy" subscribe to a theory of psychotherapy unlike our own. They stress the search for memories, the reliving of past experiences, and abreaction.[7] Our aim, on the other hand, was to facilitate the release of all the growth processes which we itemized in an earlier section of this paper. The English investigators, in particular,‡ are still preoccupied with the abreactive effects of "narcoanalysis." What we sought in our therapy, on this score, was not any sudden or uncontrolled explosion of pent-up feelings but, rather, a gradual opening of "Pandora's box." Intense abreaction we consider to be at its best only palliative, and at its worst, threatening or disorganizing in its effect on a patient.

We hold the further view that it is inaccurate or misleading in our context to refer to thiopental sodium and methamphetamine, or to any comparable combination of drugs, as mere aids or adjuncts to psychotherapy. Such terminology implies that the drug action plays the secondary or subordinate role. The drugs we employed and psychotherapy

* Lasagna, von Felsinger, and Beecher.[40] Nowlis.[41] Von Felsinger, Lasagna, and Beecher.[42] Wendt, G. R., and others: Chemical Influences on Behavior: II. Development of Methods and Preliminary Results on the Effects of Some Drugs on Emotional and Social Behavior, unpublished report, Department of Psychology, University of Rochester, May 16, 1953; III. The Effects of Dramamine and Scopolamine on Emotional and Social Behavior with Comparison Data on the Effects of Other Drugs, unpublished report, Department of Psychology, University of Rochester, March 21, 1953.

† The formulation of a really adequate theory of pharmacological psychotherapy must wait until the effect of drugs on the learning process has been subjected to a great deal of further experimentation on both the human and the animal level. References 43 to 48.

‡ References 15, 49, and 50.

as such supplement one another; they work synergistically. The evidence would seem to indicate that psychotherapy and our chemical agents, acting as a unit, accomplished together what neither could have effected alone.

It stands to reason, moreover, that the last word has not been spoken about the choice of drugs that are most effective for psychotherapy. Thiopental sodium and methamphetamine happen to be the two forms of medication that best serve our pragmatic needs at this time. With continued advances in pharmacology, this method of treatment will doubtless have still better chemical agents at its disposal.

On other grounds, we anticipate the comment that psychotherapy with the use of drugs is, at bottom, a method of treatment by suggestion. This criticism has some validity. At the same time, it would seem obvious that all methods of psychotherapy, including psychoanalysis, contain certain elements of suggestion. More than that, it is our conviction that disorders of the sort we are discussing could never be alleviated in any lasting way through the use of suggestion alone. Yet the role of suggestibility in this sphere certainly warrants controlled investigation.§ Some workers at Bellvue, meanwhile, have made a beginning in this direction.[20] These investigators report that certain of their patients became notably more responsive to psychotherapy following intravenous injections of *d*-desoxyephedrine (Methedrine), yet remained comparatively unresponsive following intravenous placebo injections. With our own patients we observed that marked changes in permeability or accessibility could oftentimes be induced when, without the patient's foreknowledge, we altered even slightly the doses of the two drugs we were employing.

Speculating in another direction, we wonder to what degree our results are affected by the sheer length of time devoted to therapy. All of our patients, it will be recalled, had had more or less protracted psychoanalyses before they came to us. The total treatment time, it might be argued, turned the trick. This order of cause and effect, we feel, is possible, but not probable.

There remains the possibility that psychotherapy with the use of the proper drugs produces only superficial or transitory change, without effecting permanent results or bringing about any basic alterations in either character structure or total adaptation. Here our results are far from definitive.

The record of our limited follow-up is as follows: With 3 of the original group of 16 cases, therapy failed completely. These patients were referred elsewhere for further psychiatric care; all three probably qualify as cases of pseudoneurotic schizophrenia or of very severe obsessive-compulsive psychoneurosis.

For the remaining 13 cases, on the other hand, sustained improvement seems to be the rule. By improvement, we mean a relatively good life adaptation—an enhanced capacity for productive work and changes in social interaction which both the patients and those with whom they are in regular contact find more or less satisfying. Of the 13 improved cases, 5 are still receiving intensive treatment; 2 are being seen once a month or less often, and 6 have terminated treatment. The terminated cases, all of whom we have followed up, have functioned on their own, without therapy, more or less successfully for an average term of 12 to 16 months.

Despite these apparent gains, we readily concede the point that Freud made long ago, i. e., that some patients, after the termination of intensive treatment, continue to require recurrent and intermittent care for years on end or for a lifetime.‖ A small proportion of our 16 cases will doubtless require such continuing therapeutic contact. Nonetheless, with the refractory disorders we were called upon to treat, pharmacological psychotherapy seemed to approach the goal of more or less lasting amelioration.

§ References 40, 41, and 42.

‖ References 51 and 52.

SUMMARY

This paper is a report on the use of pharmacological psychotherapy with 16 patients with refractory psychoneuroses and personality disorders.

The patients in question had all undergone, without success, previous psychoanalyses, over periods ranging from six months to three years.

An optimal psychophysiological state for psychotherapy was induced by employing minimum effective doses of thiopental sodium, followed by methamphetamine, administered intravenously.

Under these conditions it was possible to institute intensive psychotherapy.

Of our 16 cases, 13 showed slight to considerable improvement, in spite of the fact that the majority of the patients under consideration had moderate to severe obsessive-compulsive states as either the primary or the secondary disorder.

Limited follow-up of the 13 improved cases seems to indicate that the gains we have reported are sustained.

Pharmacological psychotherapy shows promise of becoming a method of choice for the treatment of refractory, moderate to severe psychoneuroses and personality disorders.

444 North Bedford Dr.

REFERENCES

1. American Psychiatric Association, Diagnostic and Statistical Manual: Mental Disorders, prepared by Committee on Nomenclature and Statistics, Washington, D. C., 1952.

2. Horsley, J. S.: Narco-Analysis: A New Technique in Short-Cut Psychotherapy; a Comparison with Other Methods and Notes on the Barbiturates, London, Oxford University Press, 1943; First American Edition, 1946.

3. Lindemann, E.: The Psychopathological Effects of Sodium Amytal, Proc. Soc. Exper. Biol. & Med. **28**:864-866 (June) 1931.

4. Lindemann, E.: The Psychological Changes in Normal and Abnormal Individuals Under the Influence of Sodium Amytal, Am. J. Psychiat. **11**: 1083-1091 (May) 1932.

5. Bleckwenn, W. J.: Production of Sleep and Rest in Psychotic Cases, Arch. Neurol. & Psychiat. **24**:365-372 (Aug.) 1930.

6. Bleckwenn, W. J.: Sodium Amytal in Certain Nervous and Mental Conditions, Wisconsin M. J. **29**:693-696 (Dec.) 1930.

7. Grinker, R. R.: Sedation as a Technique in Psychotherapy, Bull. New York Acad. Med. **22**: 185-203 (April) 1946.

8. Hoch, P. H.: Present Status of Narco-Diagnosis and Therapy, J. Nerv. & Ment. Dis. **103**: 248-259 (March) 1946.

9. Hoch, P. H.: Narcodiagnosis and Narcotherapy in Neuroses and Psychoses, New York J. Med. **47**:2694-2698 (Dec.) 1947.

10. Hoch, P. H.: Evaluation of Newer Pharmacodynamic Therapies, Including the Narcoanalytic Use of Drugs, in Psychiatric Treatment, S. B. Wortis, Editor, Baltimore, The Williams & Wilkins Company, 1953, pp. 239-244.

11. Hoch, P. H.; Cattell, J. P., and Pennes, H. H.: Effect of Drugs: Theoretical Considerations from a Psychological Viewpoint, Am. J. Psychiat. **108**:585-589 (Feb.) 1952.

12. Hoch, P. H., and Kalinowsky, L. B.: Shock Treatments, Psychosurgery and Other Somatic Treatments in Psychiatry, New York, Grune & Stratton, Inc., 1952.

13. Hoch, P. H., and Polatin, P.: Narcodiagnosis and Narcotherapy, in Specialized Techniques in Psychotherapy, New York, Basic Books, Inc., 1952, pp. 1-23.

14. Sargant, W.: Aims and Methods of Treatment, in Perspectives in Neuropsychiatry, London, H. K. Lewis & Co., Ltd., 1950, pp. 201-202.

15. Sargant, W., and Slater, E.: An Introduction to Physical Methods of Treatment in Psychiatry, Baltimore, The Williams & Wilkins Company, 1954.

16. Grinker, R. R., and Spiegel, J. P.: Men Under Stress, Philadelphia, The Blakiston Company, 1945.

17. Gottlieb, J. S., and Coburn, F. E.: Psychopharmacologic Study of Schizophrenia and Depressions: Intravenous Administration of Sodium Amytal and Amphetamine Sulfate Separately and in Various Combinations, Arch. Neurol. & Psychiat. **51**:260-263 (March) 1944.

18. Keane, K. M., and Kant, F.: Investigations on the Use of Cortical Stimulants with Sodium Amytal for Narcoanalysis, J. Nerv. & Ment. Dis. **117**:140-143 (Feb.) 1953.

19. Levine, J.; Rinkel, M., and Greenblatt, M.: Psychological and Physiological Effects of Intravenous Pervitin, Am. J. Psychiat. **105**:429-434 (Dec.) 1948.

20. Simon, J. L., and Taube, H.: A Preliminary Study on Use of Methedrine in Psychiatric Diagnosis, J. Nerv. & Ment. Dis. **104**:593-596 (Dec.) 1946.

21. Straker, M.: Intravenous Methamphetamine—Adjuvant to Psychotherapy, Am. J. Psychiat. **109**:853-855 (May) 1953.

22. Hargrove, E. A.; Bennett, A. E., and Steele, M.: An Investigation of Carbon Dioxide as an Adjunct to Psychotherapy in Some Neuroses, Am. J. Psychiat. **110**:844-849 (May) 1954.

23. Myerson, A.: The Reciprocal Pharmacological Effects of Amphetamine (Benzedrine) Sulfate and the Barbiturates, New England J. Med. **221**: 561-564 (Oct.) 1939.

24. Myerson, A.: The Treatment of Hysterical Amnesia by Purely Pharmacological Means, New England J. Med. **236**:821-823 (May) 1947.

25. Myerson, A.; Loman, J.; Rinkel, M., and Lesses, M. F.: Effect of Amphetamine (Benzedrine) Sulfate and Paredrine Hydrobromide on Sodium Amytal Narcosis, New England J. Med. **221**:1015-1019 (Dec.) 1939.

26. Dameshek, W.; Myerson, A.; and Loman, J.: Effects of Sodium Amytal on the Metabolism, Am. J. Psychiat. **91**:113-135 (July) 1934.

27. Round Table Conference on Sodium Pentothal, Canadian M. A. J. **61**:187-188 (Aug.) 1949.

28. Sollmann, T.: A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, Ed. 7, Philadelphia and London, W. B. Saunders & Company, 1948, pp. 684-690.

29. Tatum, A. L.: The Present Status of the Barbiturate Problem, Physiol. Rev. **19**:472-502 (Oct.) 1939.

30. Tatum, A. L.: The Pharmacology of Barbiturates, Ann. Rev. Physiol. **2**:359-370, 1940.

31. Tilkin, L.: Medical Contraindications to the Use of Sodium Pentothal for Narcosynthesis, Dis. Nerv. System **12**:57-61 (Feb.) 1951.

32. Appel, K. E.: The Present Challenge of Psychiatry, Am. J. Psychiat. **111**:1-12 (July) 1954.

33. Brosin, H., and others: Report of the Special Commission on Psychodynamic Principles, in The Psychiatrist: His Training and Development, Conference on Psychiatric Education, Washington, D. C., American Psychiatric Association, 1953, pp. 22-48.

34. Editorial: New Drugs and Psychotherapy, Am. J. Psychotherapy **9**:193-195 (April) 1955.

35. Kubie, L. S., and Margolin, S.: The Therapeutic Role of Drugs in the Process of Repression, Dissociation and Synthesis, Psychosom. Med. **7**: 147-151 (May) 1945.

36. Rioch, D. McK.: Theories of Psychotherapy, in Dennie, W., and others: Current Trends in Psychological Theory, University of Pittsburgh Press, 1951, pp. 140-164.

37. Wikler, A.: Mechanisms of Action of Drugs That Modify Personality Function, Am. J. Psychiat. **108**:590-599 (Feb.) 1952.

38. Dixon, W. J., and Massey, F. J.: Introduction to Statistical Analysis, New York, McGraw-Hill Book Company, 1951.

39. Fisher, R. A.: Statistical Methods for Research Workers, New York, Hafner Publishing Co., Inc., 1950.

40. Lasagna, L.; von Felsinger, J. M., and Beecher, H. K.: Drug-Induced Mood Changes in Man: I. Observations on Healthy Subjects, Chronically Ill Patients, and "Postaddicts," J. A. M. A. **157**:1006-1020 (March) 1955.

41. Nowlis, V.: The Development and Modification of Motivational Systems in Personality in Current Theory and Research in Motivation: A Symposium, University of Nebraska Press, 1953, pp. 114-138.

42. von Felsinger, J. M.; Lasagna, L., and Beecher, H. K.: Drug-Induced Mood Changes in Man: II. Personality and Reactions to Drugs, J. A. M. A. **157**:1113-1119 (March) 1955.

43. Bailey, C. J., and Miller, N. E.: The Effect of Sodium Amytal on an Approach-Avoidance Conflict in Rats, J. Comp. & Physiol. Psychol. **45**:205-208 (June) 1952.

44. Layman, J. W. A.: A Quantitative Study of Certain Changes in Schizophrenic Patients Under the Influence of Sodium Amytal, J. Gen. Psychol. **22**:67-86 (Jan.) 1940.

45. Lindemann, E., and Clarke, L. D.: Modifications in Ego Structure and Personality Reactions Under the Influence of the Effects of Drugs, Am. J. Psychiat. **108**:561-567 (Feb.) 1952.

46. Mainord, W. A.: Some Effects of Sodium Amytal on "Deteriorated" Schizophrenics, J. Consult. Psychol. **17**:54-57 (Feb.) 1953.

47. Masserman, J. H., and Yum, K. S.: An Analysis of the Influence of Alcohol on Experimental Neuroses in Cats, Psychosom. Med. **8**:36-52 (Jan.-Feb.) 1946.

48. Zuckerman, M.; Izner, S., and Leiser, R.: Sodium Amytal Rorschach in Incipient Schizophrenia, Dis. Nerv. System **15**:49-54 (Feb.) 1954.

49. Campbell, A. M. G.: Sodium Evipan as an Aid to Psychotherapy, Guy's Hosp. Rep. **88**:185-198, 1938.

50. Sargant, W.: Some Observations of Abreaction with Drugs, Digest Neurol. & Psychiat., Inst. of Living **16**:193-206 (April) 1948.

51. Freud, S.: New Introductory Lectures on Psycho-Analysis, translated by W. J. H. Sprott, New York, W. W. Norton & Company, 1933, p. 214.

52. Freud, S.: Analysis Terminable and Interminable, in Collected Papers, London, The Hogarth Press, 1950, Vol. 5, pp. 316-357.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

CARBOHYDRATE METABOLISM IN BRAIN DISEASE: V. EFFECT OF EPINEPHRINE ON INTERMEDIARY CARBOHYDRATE METABOLISM IN SCHIZOPHRENIC AND MANIC-DEPRESSIVE PSYCHOSES. DOROTHY H. HENNEMAN, MARK D. ALTSCHULE, ROSE-MARIE GONCZ, and PHYLLIS DAVIS, A. M. A. Arch. Int. Med. **95**:594 (April) 1955.

Carbohydrate metabolism is abnormal in patients with manic-depressive, schizophrenic, and involutional psychoses. Fasting blood glucose and lactic acid levels are frequently elevated above normal. The mobilization of glucose from hepatic glycogen after the administration of epinephrine alone is greater than normal in these psychoses except when malnutrition or psychosis has been present over a long period of time. In this study, the authors observed the effect of epinephrine upon the blood concentrations of pyruvic, citric and α-ketoglutaric acids. Lactic acid is of particular significance, since it is brought forth by epinephrine, whereas glucose is derived from the liver. Observations were made on 12 psychotic patients, 8 of whom had chronic psychoses and 4 psychoses of recent origin, and these results were compared with those for 6 normal subjects. The patients and normal controls were of comparable ages between 25 and 50 years. Three chronic psychotic patients had frontal lobotomies three to nine years previously.

The four patients with psychoses of recent onset showed rises in the blood lactic acid within the range of change found in the six normal subjects. Four of the eight patients with chronic psychoses showed changes well below this range, whereas the patients with previous lobotomies had normal changes in lactic acid concentrations. The blood pyruvic, citric and α-ketoglutaric acid concentrations were the same in all three groups of subjects. The authors conclude that the decreased rise in blood glucose and lactic acid concentrations in chronic psychotic patients after the injection of epinephrine is not specific, as these findings have been observed in chronic debilitating diseases, idiopathic epilepsy, and head injuries. The reversal of the abnormal finding in patients with chronic psychoses three to nine years after lobotomy cannot be explained. The fact that the psychoses persisted whereas the biochemical change did not emphasizes the nonspecificity of these examinations with respect to mental disease.

MANDEL, Philadelphia.

TOXIC EFFECTS OF TRI-ORTHO-CRESYL PHOSPHATE ON THE NERVOUS SYSTEM: AN EXPERIMENTAL STUDY IN HENS. J. B. CAVANAUGH, J. Neurol. Neurosurg. & Psychiat. **17**:163 (Aug.) 1954.

Cavanaugh studied the changes in the nervous system following poisoning with tri-*o*-cresyl phosphate and found degeneration of axis cylinders and myelin sheaths in both the peripheral nerves and the long tracts of the spinal cord. The degeneration appears to affect the distal extremities of the axons, and the long fibers of large diameter are particularly selected.

The author stresses the closeness with which these changes resemble those of thiamine deficiency and suggests that there may be a mechanism producing neuronal damage common to the two conditions. He has studied the relation between damage to nerve tissue and the inhibition of pseudocholesterase by tri-*o*-cresyl phosphate and concludes that this is probably not of primary significance.

ALPERS, Philadelphia.

REPETITIVE DISCHARGES FROM HUMAN MOTOR NERVES AFTER ISCHAEMIA AND THEIR ABSENCE AFTER COOLING. WILLIAM COBB and JOHN MARSHALL, J. Neurol. Neurosurg. & Psychiat. **17**:183 (Aug.) 1954.

Cobb and Marshall present further evidence on the site of origin of the repetitive discharge in (human) motor nerves following ischemia, as revealed by the electrical discharge in muscles.

It was found that during the recovery period following ischemia, produced by inflation of a pneumatic cuff around the arm, repetitive discharges are readily evoked in the first dorsal interosseous muscles by electrical stimulation of the ulnar nerve. A similar result may be obtained by local pressure, exerted by a nerve clamp on the same segment of the ulnar nerve, although, during compression, there is no evidence of interference with the general circulation of the forearm and hand. The authors conclude that the repetitive discharge arises in that segment of the nerve which has been ischemic. After a similar length of nerve has been cooled by immersion of the elbow in ice water for up to 30 minutes, no repetitive discharge can be evoked. This supports the subjective evidence that the effects of ischemia and cooling on nerves are qualitatively, and, probably, fundamentally different.

ALPERS, Philadelphia.

Meninges and Blood Vessels

WATERHOUSE-FRIDERICHSEN SYNDROME: REPORT OF A CASE WITH RECOVERY, DONALD BAHR and CHARLES LEVY, Ann. Int. Med. **42**:439 (Feb.) 1955.

Bahr and Levy describe a case of Waterhouse-Friderichsen syndrome complicating massive lobar pneumonia and lung abscess. The patients presented a typical clinical picture characterized by a prodromal phase of injection and, after a varying period, the sudden, dramatic onset of peripheral vascular collapse and petechial eruptions. These lesions rapidly become purpuric; necrosis and sloughing may follow. The patient was apprehensive and restless, and occasionally temporarily delirious. Mental lucidity was usually maintained. The anuria usually appearing in these patients, and lasting 24 to 36 hours after the onset of the syndrome, did not occur in this case. At no time did his output go below 200 cc. daily.

This patient exhibited leucocytosis with the onset of adrenal insufficiency. Though he had been ill for several days prior to admission to the hospital, his total white cell count on admission was only 5500 per cubic millimeter. Four days later this was increased to 27,000, when petechiae began to appear. The patient also showed a marked eosinophilia, with a count of 270 cells per cubic millimeter. A total eosinophile count of over 50 is considered incompatible with adequate adrenal function. The patients showed a remarkable change when started on cortisone therapy. With cortisone, massive doses of penicillin, and intravenous whole blood and glucose solutions, he made an excellent recovery. Drugs such as epinephrine, commonly used to support the blood pressure, were not found necessary, nor was desoxycorticosterone acetate or aqueous adrenocortical extract used.

ALPERS, Philadelphia.

STUDIES IN CEREBROVASCULAR DISEASE: IV. SYNDROME OF INTERMITTENT INSUFFICIENCY OF THE CAROTID ARTERIAL SYSTEM. CLARK H. MILLIKAN and ROBERT G. SIEKERT, Proc. Staff Meet., Mayo Clin. **30**:186 (May 4) 1955.

Millikan and Siekert point out that in the literature adequate emphasis has not been placed on the symptoms which frequently precede thrombosis of the internal carotid artery. They suggest that these premonitory symptoms make up a syndrome and propose that the name "syndrome of intermittent insufficiency of the internal carotid arterial system" be used. This syndrome consists of intermittent attacks of unilateral impairment of motor or sensory function or both, in certain instances associated with a disorder of speech or homolateral involvement of vision or both. Eight cases are reported here to demonstrate the variety and nature of the symptoms encountered. Millikan and Siekert suggest that patients having this syndrome be treated with anticoagulant drugs unless there is a definite contraindication to the use of such therapy.

ALPERS, Philadelphia.

MENTAL DISTURBANCES IN TUBERCULOUS MENINGITIS. MOYRA WILLIAMS and HONOR V. SMITH, J. Neurol. Neurosurg. & Psychiat. **17**:173 (Aug.) 1954.

The mental disorders seen in tuberculous meningitis were studied in adult patients both during the illness and after recovery. Williams and Smith describe the characteristic pattern of mental disorders seen once the full clinical picture has developed, together with variations in this pattern. Three separate mental states are distinguished: the confusional state, the amnesic state, and the postrecovery state. The chief characteristic of the mental changes is the predominance of the disorder of memory over the other intellectual deficits. This is seen most

clearly in the amnesic and postrecovery states. The pattern of recovery from the confusional and amnesic state is also described. The authors compare the pattern of mental disorder in tuberculous meningitis with that seen in other organic dementias, notably that following head injuries. They point out that the picture in tuberculous meningitis is sufficiently characteristic to have diagnostic importance.

ALPERS, Philadelphia.

Diseases of the Brain

NASAL GLIOMAS. FRANKLIN E. ALTANY and KENNETH L. PICKRELL, A. M. A. Arch. Surg. **71**:275 (Aug.) 1955.

According to Schmidt, nasal glioma is originally an encephalocele which has become isolated from the brain during embryonic development by closure of the fetal sutures of the skull. This theory explains well the continuous series of observations leading from a true nasal encephalocele, with an ependyma-lined ventricular cavity, to a separate solid glial mass at the bridge of the nose. In some cases, a fibrous or glial stalk to the brain can be still demonstrated. Nasal gliomas occur either extranasally or intranasally, or in both locations. Occasionally these congenital lesions have a tendency toward autonomous growth. In the clinical differential diagnosis, one must consider sebaceous or dermoid cysts, lipomata, encephalocele, nasal polyps, and cyst of the lacrimal ducts. Surgical removal of nasal glioma usually results in a complete cure.

An illustrative case report is given.

LIST, Grand Rapids, Mich.

CASE OF ACROMEGALY ASSOCIATED WITH THYROTOXICOSIS. JOHN P. HEANEY, CHARLES L. JAMES, CHARLES L. SPURR, and MICHAEL E. DEBAKEY, A. M. A. Arch. Surg. **71**:279 (Aug.) 1955.

The authors report in detail a case of acromegaly combined with thyrotoxicosis. It is noteworthy that more than one-half the patients with acromegaly show significantly increased basal metabolic rates and one-fourth exhibit an enlarged thyroid gland. The problem whether the thyrotoxicosis is an independent, coexisting condition or is secondary to hyperpituitarism has not been conclusively solved. Hypermetabolism found in cases of acromegaly cannot be explained by the presence of an associated hyperthhyroidism, but is to be considered due in part to direct action of the overfunctioning pituitary gland, for the following reasons: The radioactive iodine uptake in true hyperthryroidism is high, whereas in cases of acromegaly with hyperthyroidism it remains usually normal or low. The circulating protein-bound iodine is not elevated in acromegaly, in contrast to that in cases of true thyrotoxicosis. Hyperthyroid symptoms in acromegaly frequently fail to respond to strong iodine solution U. S. P. and to thiourea derivatives.

The increased metabolism of acromegalics may be reduced either by surgery or by irradiation of the pituitary gland. In the absence of serious pressure symptoms from pituitary tumor or from thyromegaly, it is advisable to begin the treatment with x-ray therapy of the pituitary gland. If this fails, the patient should then be subjected to total thyroidectomy, following adequate preparation with strong iodine solution U. S. P. Acromegalic patients with an enlarged larynx are more likely to need temporary tracheotomy than the average patient with thyroidectomy. There is no evidence that thyroidectomy will increase the acromegalic symptoms.

LIST, Grand Rapids, Mich.

FATAL TOXIC ENCEPHALITIS OCCURRING DURING IPRONIAZID THERAPY IN PULMONARY TUBERCULOSIS. ROGER S. MITCHELL, Ann. Int. Med. **42**:417 (Feb.) 1955.

Mitchell describes a case of fatal toxic encephalitis which occurred after six months of iproniazid therapy in a 4 to 5 mg/kg. dose. The patient was a 60-year-old man who had been treated for pulmonary tuberculosis over a period of 20 years by intermittent bed rest, aminosalicylic acid, streptomycin, and pneumoperitoneum.

For three months preceding his final acute illness the only drug taken regularly was iproniazid. There was a striking change in his appetite and in his mood, which became almost euphoric, in contrast to his usual rather anxious and depressed state. The remarkable increase in appetite resulted in a gain of 30 lb. Other symptoms, suggestive of a mild toxic effect on the central nervous system, were not considered troublesome by the patient. These were slight tremor in

the arms and legs, increased frequency of urination with some urgency, continued reduction in potency, which was already declining, some restlessness at night, and some tinnitus.

The final illness began acutely with rise in temperature, and the possibility of a tuberculous meningitis was considered because of the developing double vision, increasing headache, and motor restlessness. This clinical impression was later altered to meningoencephalitis. The patient became increasingly toxic and died 10 days after the onset of the terminal episode.

Postmortem examination was limited to the brain. There was no evidence of tuberculosis in either the brain or the meninges. The anatomic diagnoses were slight focal leptomeningeal scarring; focal subarachnoid hemorrhages; focal perivascular fresh hemorrhages in the cerebral cortex and hemosiderin deposits about the parenchymal vessels and in the meninges; slight perivascular mononuclear infiltrations associated with hemorrhage in the brain stem and cerebrum; occasional hyaline intracerebral vessels, and chromophobe adenoma, hypophysis.

Since there was no other obvious cause of toxicity, it seems reasonable to attribute the patient's death to hemorrhagic encephalitis due to a toxic effect of iproniazid.

There was one other death of a patient receiving iproniazid at Trudeau Sanatorium. In this case there was no demonstrable relationship between death and the drug. A 50-year-old man with moderately advanced pulmonary tuberculosis died very suddenly, without any warning whatsoever, on the eighth day of iproniazid therapy (4 mg/kg.). A complete autopsy, including the brain, revealed no cause for death. It was presumed that death was due to ventricular fibrillation.

The author suggests that, in view of the similarity of the symptoms displayed by these patients to those resulting from acute vitamin deficiency, the possibility exists that the two deaths reported may have occurred because of acute nicotinamide deficiency induced by iproniazid therapy.

ALPERS, Philadelphia.

MENINGIOMA OF THE CHOROID PLEXUS ARISING FROM THE LATERAL VENTRICLE. JACK DUNN JR. and WINCHELL MCK. CRAIG, Proc. Staff Meet. Mayo Clin. **29**:577 (Oct. 27) 1954.

Meningioma arising from the choroid plexus is one of the rarer forms of intracranial tumor. It occurs more frequently in the left lateral ventricle and is most likely to develop in females. Dunn and Craig describe the symptoms, clinical findings, and diagnostic procedures in a 33-year-old woman who on operation was found to have a large meningioma arising from the choroid plexus of the left lateral ventricle.

The authors refer to a recent review of this condition by Wall, who enumerated the salient symptoms as follows: 1. The most frequent symptom is headache, which, since it is caused by increased intracranial pressure, is not characteristic. 2. Contralateral motor or sensory impairment was found in 70% of cases, with convulsive seizures recorded rarely. Dunn and Craig's patients had convulsive seizures. 3. Homonymous hemianopsia, usually involving the lower quadrants, appeared in 60% of the cases, visual hallucinations in the blind fields being rare. 4. Twenty-five per cent of the patients had such signs as ataxia or nystagmus, suggesting a cerebellar lesion. The ataxia was always found on the side opposite the tumor. 5. Difficulty in speech or reading was infrequently noted. 6. Occasionally paresthesias in the distribution of the trigeminal nerve on the affected side was noted. Electroencephalography, pneumoventriculography, and angiography may be helpful as diagnostic aids.

Although these tumors may be totally removed surgically, certain persistent neurologic deficits may follow because of the location of the tumor. Wall noted postoperatively an immediate increase in speech disturbance, hemiparesis, impairment of discriminative sensation, and homonymous hemianopsia. He found, as did the authors in the case here reported, a rapid resolution of the hemiparesis, more delayed return of discriminative sensation, and slower restitution of the heminanoptic defects.

ALPERS, Philadelphia.

Diseases of the Spinal Cord

CERVICAL SPONDYLOSIS. SIR RUSSELL BRAIN, Ann. Int. Med. **41**:439 (Sept.) 1954.

There are three main sites of intervertebral disc protrusion in the cervical region: (1) dorsomedial, (2) dorsolateral, and (3) intraforaminal. The main factor in the causation of cervical disc degeneration is age, and a large majority of patients are over the age of 50. Congenital

abnormalities, the great mobility of the cervical spine, and previous trauma are contributing factors in the process of disc degeneration.

Cervical spondylosis may cause damage to the spinal nerve roots or the spinal cord or both. The narrowing of the intervertebral disc itself, osteophytes extending into the foramen, the obliteration of the root sleeve by fibrous tissue, and the interference with the blood supply of the roots are all contributing factors. The effect of these various factors on the cord is to produce patches of demyelination with ascending and descending degeneration. The pathologic changes are a myelopathy or, in severe cases, a myelomalacia. In the majority of cases the cerebrospinal fluid is normal in dynamics and composition.

From a comparison of the radiologic, operative, and pathologic findings, Brain stresses four general conclusions: 1. Radiographic evidence of a narrowed intervertebral disc is not evidence of a disc protrusion. 2. Similarly, radiographic evidence of a narrowed intervertebral foramen is not evidence of compression of the corresponding nerve roots. 3. The presence of an intervertebral foramen which is normal radiographically is not evidence that the corresponding nerve roots are also normal, since they may be the site of root sleeve fibrosis. 4. Cervical spondylosis is not necessarily the cause of associated symptoms of nervous disease, even when these are evidence of a lesion of the spinal cord in the cervical region.

In treatment, the author advocates immobilization of the neck, first, with a plaster collar and, after a few weeks, with a plastic one, which must be worn for several months. He has not been impressed with the value of traction in chronic cervical spondylosis, and believes that manipulation is a dangerous mode of treatment. Surgery is most likely to be successful when the patient is relatively young, when the history is relatively short, when the disc protrusion is single rather than multiple, and when the cardiovascular system is normal. Decompression is favored as the surgical procedure, and when there is abnormal mobility of the intervertebral joints, fusion may be indicated.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

VERTIGO (MÉNIÈRE) FOLLOWING RADIAL MASTOIDECTOMY: TREATMENT BY TYMPANIC PLEXECTOMY. SAMUEL ROSEN, A. M. A. Arch. Otolaryng. **60**:302 (Sept.) 1954.

Rosen describes five cases in which vertigo developed following a radical mastoidectomy in which the chorda tympani nerve had also been sacrificed. The episodes of vertigo persisted from a few months to several years after the radical mastoidectomy. In all five cases, taste was absent on the anterior two-thirds of the tongue on the side of the operation because of division of the chorda tympani nerve. The ear not operated on was normal.

The five patients ranged in age from 40 to 53 years, and the description of vertigo given by them was similar to that described by Ménière. The patients were in good health and had no evidence of cardiovascular disease, multiple sclerosis, eighth-nerve tumor, syphilis, or drug intoxication.

The tympanic plexus was sectioned in all five cases through a large ear speculum in the already widened external auditory canal. The vertigo ceased promptly after the tympanic plexus was sectioned.

The author suggests the hypothesis that the tympanic plexus, as well as the chorda tympani, carries afferent impulses to a sensory nucleus which has functional interconnection with the vestibular nucleus, and the abnormal activity of these afferents causes the vertigo. Division of these afferents is assumed to be responsible for the disappearance of the vertigo.

ALPERS, Philadelphia.

CANICOLA FEVER WITH NEUROLOGICAL COMPLICATIONS. J. E. MIDDLETON, Brit. M. J. **2**:25 (July 2) 1955.

Middleton reports a case of canicola fever contracted from a pet dog in which treatment with chlortetracycline cured the infection but convalescence was complicated by cervical radiculitis, characterized by paralysis of the right serratus anterior and right diaphragm, transient paresis of the left thumb, and initial subjective sensory changes over the left forearm. Complete recovery did not occur until 18 months after onset of the illness. Middleton points out that, although

neurological symptoms are common in canicola fever, neurological complications are rare. He believes that the case reported is a further example of the shoulder-girdle syndrome, presumably due to hypersensitivity reaction to the infection.

ECHOLS, New Orleans.

Treatment, Neurosurgery

CEREBRAL HEMISPHERECTOMY FOR CONTROL OF INTRACTABLE CONVULSIVE SEIZURES. L. A. FRENCH, D. R. JOHNSON, I. A. BROWN, and F. B. VAN BERGEN, J. Neurosurg. **12**:154 (March) 1955.

Cerebral hemispherectomy was used in eight institutionalized children who had infantile hemiplegias with intractable seizures. This operation was an outgrowth of the procedure used to control seizures in a 38-year-old man with status epilepticus following removal of a left parietal glioma. The ages varied from 13 to 38 years, and each case was studied by pneumoencephalography or arteriography, which revealed evidence of a dilated ventricle on the affected side, porencephalic cysts, or atresia of the middle cerebral vessels. At operation, all the structures peripheral to the thalamus were removed, and great care was taken to insure removal of the hippocampus and orbital gyrus. The gross abnormalities included meningeal scarring, subarachnoid cysts, and extensive vascular malformations.

All patients except the man with the glioma previously mentioned had had uncontrollable seizures that made institutionalization necessary. Four patients have had no seizures and are not receiving medication. Three others have had one seizure each, all occurring within the first few months after operation, and each is now taking only small doses of anticonvulsants. One patient had five seizures postoperatively, but none within the last two years, and the last case was regarded as a failure, that of a microcephalic adolescent of 17 who averaged 700 to 800 grand mal seizures yearly, but still continued to have 70 seizures yearly in spite of hemispherectomy. The operation had no effect upon any preexisting neurological deficits, nor did it result in any intellectual impairment. Many patients have shown a definite improvement in their personality adjustment.

MANDEL, Philadelphia.

Muscular System

MYASTHENIA GRAVIS. F. R. FERGUSON, E. C. HUTCHINSON, and L. A. LIVERSEDGE, Lancet **2**:636 (Sept. 24) 1955.

Ferguson and his colleagues report their therapeutic experience with 85 cases of myasthenia gravis seen during the period of 1932 to 1954 in an attempt to compare the results of thymectomy and the medical treatment. First, they conclude that, although 9 of their 85 patients have died, and a further 6 have not been traced, the survival of 60, of whom 42 were in full work, suggests to them that the adjective "gravis" is not applicable to all cases of myasthenia. They are of the opinion that the diagnosis myasthenia need not be regarded as an automatic indication for thymectomy as a life-saving or urgent procedure. A period of observation, with treatment with neostigmine, may indeed prove the correct and safest form of management for many patients. If the condition is initially ocular in distribution and remains so for two or three years, they conclude that there is a good chance that the disorder will remain local and will produce little or no disability. In such cases thymectomy may not be justified. A decision to advise thymectomy may be made if the condition is generalized at an early age and cannot be controlled adequately with neostigmine. Furthermore, the extension of the ocular form to the generalized type of myasthenia gravis might also appear to be an indication for operative treatment. They state that no conclusions may be drawn from the small series of 10 cases treated surgically. Six of the patients operated upon are dead, and the manner of their death was myasthenic, with either respiratory crises or sudden syncope.

YASKIN, Camden, N. J.

Encephalography, Ventriculography and Roentgenography

VERTEBRAL ARTERIOGRAPHY OF THE BRAIN. H. F. PLAUT, Am. J. Roentgenol. **74**:226 (Aug.) 1955.

Vertebral angiography is indicated in tumors and vascular lesions involving the posterior fossa, the brain stem, or the lobes of the brain supplied by the vertebral arteries. Plaut studied

the arteries of 20 brains by dissection of the brains and studied 15 brains by performing vertebral angiograms on cadavers. He has described and illustrated by diagrams the normal course and distribution of the branches of the vertebral artery within the skull as seen in the lateral and the fronto-occipital (Chamberlain-Towne) projections of the skull. Plaut considers the Chamberlain-Towne projection as the one view that probably gives the most information in studies of the vertebral artery, although lateral views and submentovertical views may also contribute important information. He emphasizes that asymmetry of the arterial courses and calibers is found to be the rule rather than the exception when comparing the right and the left vertebral arteries in the Chamberlain-Towne projection.

WEILAND, Grove City, Pa.

INCIDENCE AND COMPOSITION OF RADIOPAQUE DEPOSITS IN THE BASAL GANGLIA OF THE BRAIN. J. A. WAGNER, U. T. SLAGER, J. M. DENNIS, and E. V. BARNES, Am. J. Roentgenol. **74**:232 (Aug.) 1955.

The authors received the whole specimens of the brains from 200 consecutive routine autopsies. Sections of these brains of uniform and consistent location were obtained from the area of the basal ganglia. These sections were roentgenographed, using a standard technique, and then they were studied histologically. Radiopaque deposits were found bilaterally in the region of the basal ganglia in only 4 of the 200 brains. None of the four patients had had skull roentgenograms. Sixty-eight per cent of the 200 cases showed vascular basophilic granular deposits in the basal ganglia when observed histologically. All of these deposits were found on histochemical examination to contain iron, but very few of them contained calcium. Among the few which contained calcium were all four in which the radiopaque deposits were exhibited in the roentgenograms. The authors conclude that the presence of radiopacity is correlated with the histochemical demonstration of calcium, but not with that of iron.

WEILAND, Grove City, Pa.

Books

Clinical Psychiatry. By W. Mayer-Gross, Eliot Slater, and Martin Roth. Price, $10. Pp. 652, with illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1955.

There has long been a need in the field of clinical psychiatry for a textbook that is critical, constructive, and complete, and that utilizes all that is new and valuable in psychiatric theory and practice. Unfortunately, this book, by three British psychiatrists, does not fill that need.

This volume is, to say the least, very spotty. There are many shrewd criticisms of some current ideas, but they are often followed by statements that are little more than nonsense. The authors feel that psychiatry belongs to medicine and that there is need for more self-criticism. They then state that the type of expansion of the scope of psychiatry as produced by the study of sociology and anthropology is bad. They feel that in the major psychiatric disorders the specific factors in causation are of a constitutional and physiopathological kind. "An experience which is shared by all human beings cannot be the cause of a difference between some human beings and others." The authors are in favor of a multidimensional approach to the field, but they want everything to be considered important to be statistically more significant in the ill than in the healthy, thus tending to rule out many factors that may be vital but not statistically impressive. Interpersonal relationships, emotional factors in precipitation of schizophrenia, etc., are vigorously deemphasized, and great stress is put on genetic and constitutional factors in most clinical syndromes. This is grossly in contrast with current thinking in therapeutic centers in this country. The American school of psychiatry is exemplified by quotations from Lidz and Lidz, but these appear somewhat distorted by their appearance out of context.

Throughout the book runs a vigorous denial and deemphasis of many of the views of Freud and his followers. Attributed to the current Freudian view are many ideas practicing analysts have long since modified or discarded. On page 17, Freudian psychology is reduced to "faith healing." Psychoanalysis is said to be "a mechanistic mythology which is far behind what contemporary psychology has to offer." And yet in the midst of this condemnation of psychoanalytic psychiatry, which runs like a theme throughout the book, are some valid warnings about the value of repeated examinations of theories in use, and some good criticism of Freud's earlier ideas. Still, there is a seeming lack of understanding of some of the analytic theories, e. g., as to what Freud meant by sexual instincts. The authors describe analytic theory as built on clinical experience with hysterics, and imply that this is all it is built on. One explanation given for the appeal analysis has in America is that the psychoanalytic approach "is of a mechanistic and deterministic type which suits well a society based on the exploitation of the machine." One wonders how the authors would describe Industrial England.

A plea is made for the reader not to accept as general any partial or narrow theory, and yet the authors tend to reject a theory if it explains only part of a phenomenon, even if intended to explain only part. There is relatively little material about therapy in this book, and then it is often general, brief, vague, and occasionally very naïve.

There is, however, much that is of value in this book. It is well organized, thorough, and well published. Descriptive material is excellent. The sections on chemical intoxications, mental disorders in trauma, and mental disorders of the aged are especially good. There is an interesting section on administrative and legal psychiatry in which procedures in different countries are compared and contrasted. Some warnings expressed are most timely. The correct need for control studies in the field is properly emphasized. An acquaintance with the literature of all schools of thought in psychiatry is displayed, and yet the emphasis on constitutional and genetic factors makes the authors' approach much more one-sided than a critical book in the present day should be.

Modern psychiatry is dynamic psychiatry. With regret, it must be stated that the good textbook of dynamic psychiatry has yet to be written.

A Textbook of Neurology. By H. Houston Merritt, M.D. Price, $12.50. Pp. 746, with 181 illustrations and 128 tables. Lea & Febiger, 600 Washington Sq., Philadelphia 6, 1955.

The purpose of this text is the presentation of the study of neurologic diseases as an integrated part of a whole, internal medicine. As such, Dr. Merritt has succeeded to an amazingly full extent. His constant approach is that of a disease entity in its broadest scope, the differences being noted as they appear in each nosological classification.

In his preface, the author states that the reason for the departure from the usual textbook of neurology (in the omission of the sections on neuroanatomy, neurologic examination, and diagnosis) is for the purpose of space conservation and because, at best, these could be but inadequately covered. In view of this, the book has considerable value for the practicing physician and for the medical student who has either a fair command of neurologic finesse or ready access to a good outline of neurologic examination. The material included is actually of considerable value to student, house officer, and practitioner, for that which is treated represents entities encountered commonly on hospital wards and in office practice. The feature for special mention is the extraction of various tables and charts from the recent literature to illustrate graphically particular statistical points, such as relative incidences of diseases and tumors, age groups, pathology, anatomical sites, and combinations of clinical findings. These are spread liberally throughout the text and give unusual enlightenment to whatever subject matter they illustrate, highlighting it in graphic form. The subjects taken up are listed according to etiology; and in the matters of neurosyphilis, cerebrovascular disease, tumors, demyelinating diseases, and the convulsive disorders Dr. Merritt reveals his particular forte. The practicing physician can utilize the sections on therapy in office practice, for they are adequate and lucid. The bibliography at the end of each section enables the interested reader to consult the pertinent key articles and to expand therefrom if he so desires. The index has been prepared as a practical guide in differential diagnosis.

La Tentative de suicide. By Dr. Pierre-B. Schneider. Price not stated. Pp. 291. Delachaux & Niestle, 32 Rue de Grenelle, Paris, 1954.

In his introduction, the author theorizes about the definition "suicide attempt" and considers the act as such only if it is conscious, and willful, aiming toward self-destruction as a means to a goal, and the person survives the atempt. This excludes the suicide attempt of the schizophrenic and of those in a state of intoxication or confusion. He accepts Esquirol's claim that every normal person at some time in his life—while on a bridge or precipice—has had an urge to kill himself.

He criticizes the statistical approach that takes into consideration only the age, sex, matrimonial status, month of the year, economic background, and other external factors, but ignores the motivation. Such statistics are particularly misleading when unsuccessful and successful attempts are put together. Of course, only in suicidal failures can one interview the attemptee and discover the dynamics of the urge.

In evaluation of the literature on suicide attempts by countries, the works written by Americans are singled out by the author for special commendation because of their emphasis on the psychoanalytical approach. The studies of Bender and Schilder, Farrar, Raphael, Arieff, Lendrum, and Moore are cited.

In his final conclusion, the author claims that, contrary to popular opinion, the number of suicide attempts is decreasing throughout the world. He also rejects Freud's view that subconsciously the suicide feels that he does not destroy himself but that he passes to another type of existence. Sane people do not think this way. Heredity plays no predispositional part. The author makes us feel that the deep reasons for suicide attempts have still to be discovered.

Appalachian Hall

ESTABLISHED 1916
Asheville, North Carolina

An Institution for the diagnosis and treatment of Psychiatric and Neurological illnesses, rest, convalescence, drug and alcohol habituation.

Insulin Coma, Electroshock and Psychotherapy are employed. The Institution is equipped with complete laboratory facilities including electroencephalography and X-ray.

Appalachian Hall is located in Asheville, North Carolina, a resort town, which justly claims an all around climate for health and comfort. There are ample facilities for classification of patients.

WM. RAY GRIFFIN, JR., M.D.
ROBERT A. GRIFFIN, M.D.
MARK A. GRIFFIN, SR., M.D.
MARK A. GRIFFIN, JR., M.D.

For rates and further information write APPALACHIAN HALL, ASHEVILLE, N. C.

THE SOUTHARD SCHOOL

Intensive individual psychotherapy in a residential school, for children of elementary school age with emotional and behavior problems.

THE MENNINGER CHILDREN'S CLINIC

Outpatient psychiatric and neurologic evaluation and consultation for infants and children to eighteen years.

Department of Child Psychiatry

THE MENNINGER FOUNDATION

J. Cotter Hirschberg, M.D., Director

Topeka, Kansas; Telephone 3-6494

MARY POGUE SCHOOL, Inc.

Complete facilities for training, educationally and socially, the retarded and epileptic. Girls from 8 and boys from 4 — separate living accommodations.

Small classes. Individual assistance. Physical and occupational therapy and recreational programs.

Long term residential care available.

Institutional member I.H.A. and A.H.A.

Catalogue on request.

G. H. Marquardt, M.D.
Medical Director

Barclay J. MacGregor
Registrar

65 Geneva Road, Wheaton, Ill. (near Chicago)

North Shore Health Resort

on the shores of Lake Michigan

WINNETKA, ILLINOIS

NERVOUS and MENTAL DISORDERS
ALCOHOLISM and DRUG ADDICTION

Modern Methods of Treatment

MODERATE RATES

Established 1901
Licensed by State of Illinois

Fully Approved by the
American College of Surgeons

SAMUEL LIEBMAN, M.S., M.D.
Medical Director

225 Sheridan Road **Winnetka 6-0211**

Heart Attack. Walter Modell. 12 pages. 15 cents.

Varicose Veins. Morris Friedell. 8 pages. 15 cents.

They're Beating the Devil Out of Epilepsy. Paul de Kruif. 4 pages. 10 cents.

The Boom in Backaches. Robert D. Potter. 12 pages. 15 cents.

Gallstones. Harry Gauss. 8 pages. 15 cents.

Goiter. Phoebe M. Walters. 12 pages. 15 cents.

What Specialists Know About Sinusitis. Noah D. Fabricant. 4 pages. 10 cents.

Pamphlets

FOR YOUR PATIENTS

All About Hernia. John E. Eichenlaub, M.D. 8 pages. 10 cents.

The Facts About Smoking. Robert Maris. 8 pages. 15 cents.

Please remit with order

AMERICAN MEDICAL ASSN.
535 N. Dearborn St. • Chicago 10

"Beverly Farm"

INCORPORATED
Founded 1897
INCORPORATED 1922

11 buildings
220 acres of land
300 feet above
Mississippi River

HOME AND SCHOOL FOR
Nervous and Backward Children

Can accommodate 200 children, with contemplated educational improvements for a larger number. Can accept some suitable case for life.

Address all communications to **DR. GROVES B. SMITH, SUPERINTENDENT**
"Beverly Farm" **GODFREY, MADISON COUNTY, ILLINOIS**

RIVER CREST SANITARIUM

FOR

NERVOUS, MENTAL, AND ALCOHOLIC PATIENTS

Layman R. Harrison, M.D.
Physician in Charge

Martin Dollin, M.D.
Clinical Director

Russell N. Carrier, M.D.
Consultant in Psychotherapy

Arthur Gordon, M.D.
Consultant in Medicine

Katherine C. Kindred
Administrator

Approved for resident training in Psychiatry

A private hospital for the care and treatment of nervous and mental disorders. All accepted types of treatment available. Individualized attention to psychotherapy, insulin and electroshock therapy.

A cottage maintained expressly for elderly women with problems of senility and continued care. We also have accommodations for men requiring continued care.

River Crest is located in a beautifully wooded and landscaped park of about twelve acres, secluded but easily accessible by subway, bus or private car.

Full cooperation with referring physicians, who will find it convenient to visit or participate in the treatment of their patients while at River Crest.

Ditmars Boulevard and 26th Street
ASTORIA, L. I., NEW YORK CITY
AS 8-0820

TWENTY MINUTES FROM TIMES SQUARE

ADAMS HOUSE

Established 1877

☆

A non-commitment sanitarium and clinic, club-like in physical setting and atmosphere, applying re-educational psychotherapeutic methods in the study and treatment of the **psychoneuroses** exclusively.

Located in suburban Boston contiguous to and overlooking the Arnold Arboretum

☆

James Martin Woodall, M.D., Medical Director

990 CENTRE STREET, BOSTON,
Jamaica Plain, MASS.

BALDPATE, INC.

Georgetown, Mass.

Geo. 2131

Located in the hills of Essex County, 30 miles north of Boston

For the treatment of psychoneuroses, personality disorders, psychoses, alcoholism and drug addiction.

Psychotherapy is the basis of treatment; electric shock treatments, subcoma and deep coma insulin therapy when indicated; sleep treatment for withdrawal of narcotics.

Occupation under a trained therapist, diversions and outdoor activities.

G. M. SCHLOMER, M.D.
Medical Director

HIGHLAND HOSPITAL, INC.

Founded in 1904 **Asheville, North Carolina**

Affiliated with Duke University

A non-profit psychiatric institution, offering modern diagnostic and treatment procedures —insulin, electroshock, psychotherapy, occupational and recreational therapy—for nervous and mental disorders.

The Hospital is located in a seventy-five acre park, amid the scenic beauties of the Smoky Mountain Range of Western North Carolina, affording exceptional opportunity for physical and nervous rehabilitation.

The OUT-PATIENT CLINIC offers diagnostic services and therapeutic treatment for selected cases desiring non-resident care.

R. CHARMAN CARROLL, M.D.
Diplomate in Psychiatry
Medical Director

ROBT. L. CRAIG, M.D.
Diplomate in Neurology and Psychiatry
Associate Medical Director

HIGH POINT HOSPITAL

Port Chester, New York
WEstmore 9-4420

Emphasis is on analytically oriented psychotherapy, each patient receiving a minimum of three therapeutic hours per week. Other forms of treatment available adjunctively; therapy administered by attending psychoanalysts, and residents in advanced training under the immediate supervision of the director; staff of medical and surgical consultants; near New York City.

Alexander Gralnick, M.D., F.A.P.A.
Director

William V. Silverberg, M.D., F.A.P.A.
Chief Consultant in Psychotherapy

Stephen P. Jewett, M.D.
Chief Consultant in Clinical Psychiatry

Licensed by New York State Dept. Mental Hygiene

Combine your own clinical experience with the knowledge of experts . . .

by reading

- **A.M.A. Archives of DERMATOLOGY**
- **A.M.A. Archives of PATHOLOGY**
- **A.M.A. Archives of INDUSTRIAL HEALTH**

Write To:
Subscription Department

American Medical Association
535 N. Dearborn Street
Chicago 10, Ill.

HALL-BROOKE

An Active Treatment Hospital

A licensed private hospital devoted to active treatment, analytically-oriented psychotherapy, and the various somatic therapies.

A high ratio of staff to patients.

Large occupational therapy building with a trained staff offers complete facilities for crafts, arts and recreation. Full program of outdoor activities.

Each patient is under constant, daily psychiatric and medical supervision.

Located one hour from New York on 120 acres of Connecticut countryside.

HALL-BROOKE

Greens Farms, Box 31, Conn., Tel.: Westport, CApital 7-5105

George S. Hughes, M.D.
Leo H. Berman, M.D.
Alfred Berl, M.D.
Louis J. Micheels, M.D.
Robert Isenman, M.D.
Blanche Glass, M.A.
Mrs. Heide F. Bernard and
Samuel Bernard, Administrators

NEW YORK OFFICE, 46 East 73 Street
Telephone: Lehigh 5-5155

A.M.A. SPECIALTY JOURNALS REACH THE CORE OF SPECIALIZED PRACTICE . . . *Subscribe NOW to:*

→ **A.M.A. Archives of INTERNAL MEDICINE**
→ **A.M.A. Archives of PATHOLOGY**
→ **A.M.A. Archives of OPHTHALMOLOGY**

Write to:

THE AMERICAN MEDICAL ASSOCIATION
535 North Dearborn Street
Chicago 10, Illinois

RING SANATORIUM

***Eight Miles from Boston*—Founded 1879**

For the study, care, and treatment of emotional, mental, personality, and habit disorders.

On a foundation of dynamic psychotherapy all other recognized therapies are used as indicated.

Cottage accommodations meet varied individual needs. Limited facilities for the continued care of progressive disorders requiring medical, psychiatric, or neurological supervision.

Full resident and associate staff. Courtesy privileges to qualified physicians.

BENJAMIN SIMON, M.D.
Director

CHARLES E. WHITE, M.D.
Assistant Director

Arlington Heights, Massachusetts

MIssion 8-0081

A NEW SERIES IN

SEX EDUCATION

Titles in the new series

- PARENTS' PRIVILEGE
  for parents of young children of pre-school and early school age
- A STORY ABOUT YOU
  for children in grades 4, 5, and 6
- FINDING YOURSELF
  for boys and girls of approximately junior high school age
- LEARNING ABOUT LOVE
  for young people of both sexes (about 16 to 20 years of age)
- FACTS AREN'T ENOUGH
  for adults who have any responsibility for children or youth that may create a need for an understanding of sex education

PRICES

Note: Discounts apply to quantities of any single title, or to quantities of sets.

Quantity	Discount	Price
1	—	$ .50
10	10%	4.50
25	30%	8.75
50	40%	15.00
100	50%	25.00
1000	60%	200.00

Set of 5 titles, $2.25.

Distributed By

Order Department

AMERICAN MEDICAL ASSOCIATION

535 N. Dearborn St.

Chicago 10, Ill.

ORDER BLANK

Enclosed is $_____ (no stamps) for the following pamphlet(s):

Title	Quantity
1. PARENTS' PRIVILEGE	
2. A STORY ABOUT YOU	
3. FINDING YOURSELF	
4. LEARNING ABOUT LOVE	
5. FACTS AREN'T ENOUGH	
Complete set of five	

Please send pamphlet(s) to:
(Please Print)

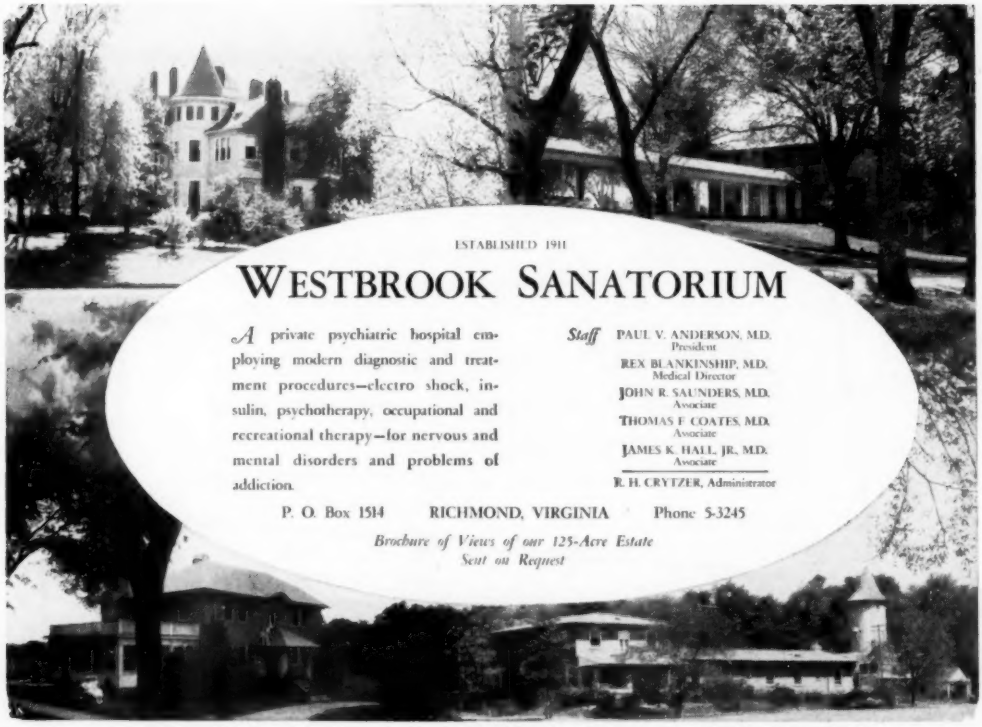
Name_____

Street_____

City_____

Zone_____ State_____

AN 1-56



ESTABLISHED 1911

WESTBROOK SANATORIUM

A private psychiatric hospital employing modern diagnostic and treatment procedures—electro shock, insulin, psychotherapy, occupational and recreational therapy—for nervous and mental disorders and problems of addiction.

Staff PAUL V. ANDERSON, M.D.
President
REX BLANKINSHIP, M.D.
Medical Director
JOHN R. SAUNDERS, M.D.
Associate
THOMAS F. COATES, M.D.
Associate
JAMES K. HALL, JR., M.D.
Associate
R. H. CRYTZER, Administrator

P. O. Box 1514 RICHMOND, VIRGINIA Phone 5-3245

Brochure of Views of our 125-Acre Estate Sent on Request

FAIRVIEW *Sanitarium*

2828 S. PRAIRIE AVE.
CHICAGO
Phone VIctory 2-1650
J. DENNIS FREUND, M.D.
Medical Director

DEVOTED TO THE ACTIVE TREATMENT OF

MENTAL and NERVOUS DISORDERS

Specializing in Psycho-Therapy, and Physiological therapies including:

- **Insulin Shock**
- **Electro-Shock**
- **Electro-Narcosis**
- **Out Patient Shock Therapy Available**

ALCOHOLISM Treated by Comprehensive Medical-Psychiatric Methods.

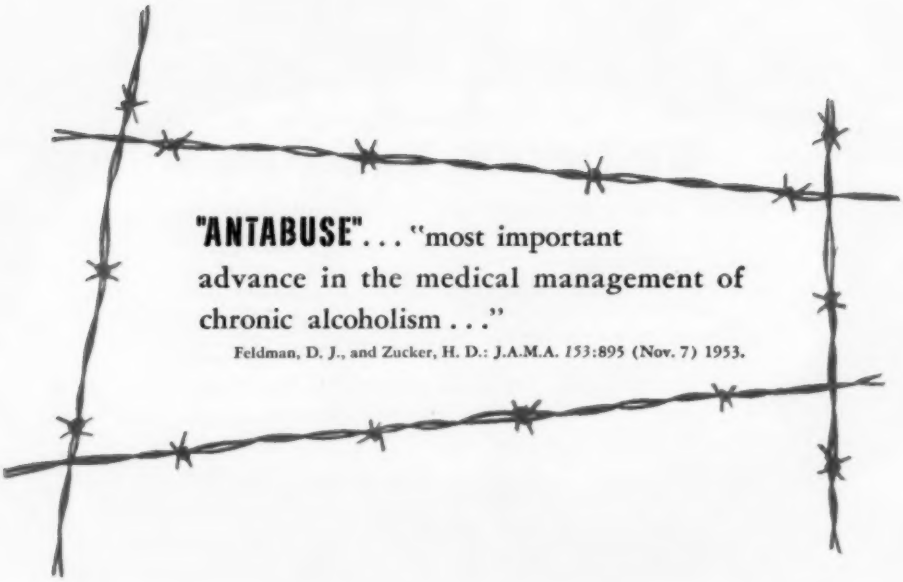
THE LIVERMORE SANITARIUM and PSYCHIATRIC CLINIC

Livermore, California
Telephone: 313
Oakland Office—411 30th Street

FOR THE TREATMENT OF NERVOUS AND MENTAL DISORDERS

THE OPEN CONVALESCENT DEPARTMENT, for nervous and general patients; the COTTAGE DEPARTMENT, for mental patients. Features: near Oakland and San Francisco; ideal climate; large beautiful grounds; hydrotherapy, athletic and occupational departments; clinical laboratory; large nursing force. Rates include room, suitable diet, medical care, general nursing and routine examinations.

HERBERT E. HARMS, M.D.—Superintendent



A "CHEMICAL FENCE" FOR THE ALCOHOLIC. "Antabuse" gives the patient a forceful and immediate reason for not drinking . . . he finds he cannot drink without experiencing extreme discomfort. By keeping the patient away from alcohol, "Antabuse" serves as a valuable adjunct to psychotherapeutic measures.

"Antabuse"® brand of DISULFIRAM (tetraethylthiuram disulfide) is supplied in 0.5 Gm. tablets, bottles of 50 and 1,000.

Complete information available on request.

Ayerst Laboratories • New York, N.Y. • Montreal, Canada

5547

PAIN

Its Mechanisms and Neurosurgical Control

By

JAMES C. WHITE, M.D., F.A.C.S.
Chief of Neurosurgical Service, Massachusetts General Hospital
Associate Professor of Surgery, Harvard Medical School

and

WILLIAM H. SWEET, M.D., F.A.C.S.
Associate Visiting Neurosurgeon, Massachusetts General Hospital
Associate Clinical Professor of Surgery, Harvard Medical School

With assistance in the psychiatric sections of Chapters IV and X from

STANLEY COBB, M.D.
Chief of Psychiatric Service, Massachusetts General Hospital
Bullard Professor of Neuropathology, Harvard Medical School

and

FRANCES J. BONNER, M.D.
Assistant in Psychiatry
Massachusetts General Hospital and Harvard Medical School
Boston, Massachusetts

"This book is concerned with pain not as a warning signal but with pain as an enemy that can be defeated. Medicinally unrelievable pain works to such a degree on man's emotions, so reduces his usefulness to himself and others, so saps his morale that we must rehabilitate him if we can. An authoritative book like this on the means by which to do it is invaluable. Its virtue is that it has been written out of rich experience. This is no 'scissors and paste' affair. On the contrary, the writers only give their approval to such operative steps as they have themselves treated and have found to fit the case."—From the Foreword by Sir Geoffrey Jefferson.

This unusually extensive experience with a full account of complications and disappointments, as well as the large proportion of gratifying successes, should be a great help to others—to the neurosurgeon who has to do the operation, to the doctor who hopes to free his patient of chronic suffering, and to the student of pain in particular and sensation in general.

Written for neurosurgeons and all who are interested in relief of persistent unbearable pain in which there is no possibility of eliminating the underlying cause.

776 pages *203 illustrations*

$17.50, postpaid

CHARLES C THOMAS • PUBLISHER
Springfield • Illinois

Important books in this field . . .

Delafresnaye—BRAIN MECHANISMS AND CONSCIOUSNESS ('55), 564 pp., 154 il., Cloth, $8.50

Elliott, Page, and Quastel—NEUROCHEMISTRY: The Chemical Dynamics of Brain and Nerve ('55), 916 pp., 101 il., Cloth, $19.50

Glees—NEUROGLIA MORPHOLOGY AND FUNCTION ('55), 115 pp., 45 il., Price Indefinite

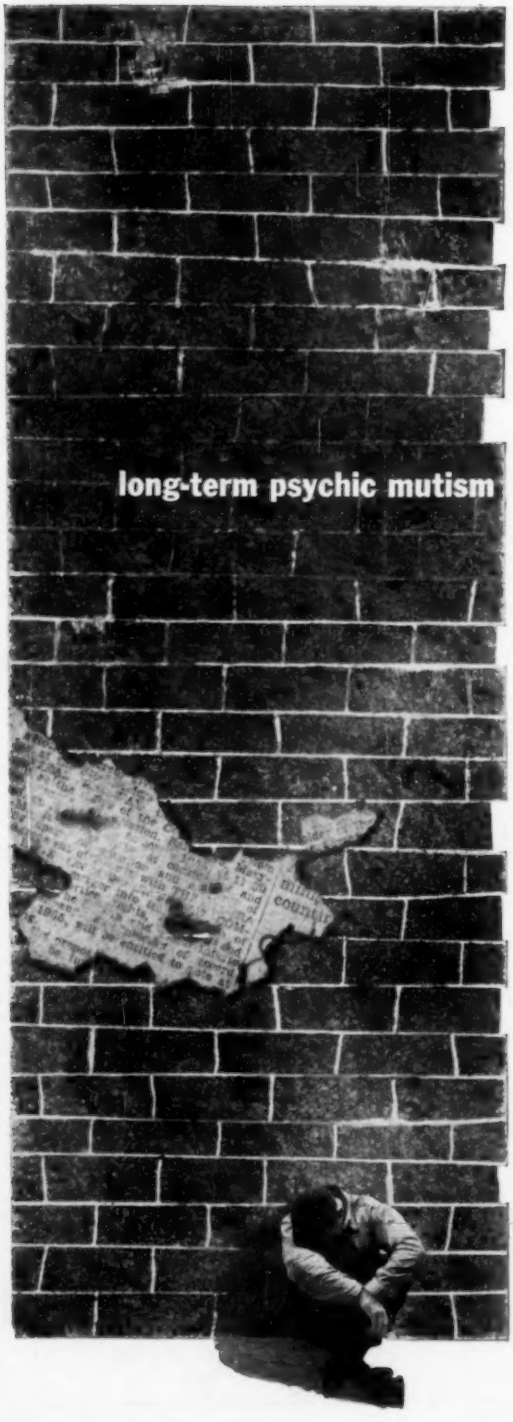
Greenfield—THE SPINOCEREBELLAR DEGENERATIONS ('55), 122 pp., 18 il., Cloth, $4.00

Kahn, Bassett, Schneider, and Crosby—CORRELATIVE NEUROSURGERY ('55), 416 pp., 355 il., Cloth, $19.50

Michaels—DISORDERS OF CHARACTER: Persistent Enuresis, Juvenile Delinquency and Psychopathic Personality ('55), 152 pp., 10 tables, Cloth, $4.75

Moore—HYPEROSTOSIS CRANII: Stewart-Morel Syndrome; Metabolic Craniopathy; Morgagni's Syndrome; Stewart-Morel-Moore Syndrome (Ritvo); Le Syndrome de Morgagni-Morel ('55), 260 pp., 129 il., Cloth, $10.50

Singer and Yakovlev—THE HUMAN BRAIN IN SAGITTAL SECTION ('55), 62 pp., 46 pages, Cloth, $7.75



long-term psychic mutism has responded to 'Thorazine'

The response to 'Thorazine' "is at times striking and dramatic, particularly in psychotic persons who have been mute and begin to communicate verbally after having given up the function for periods of 5 to 10 years."
Goldman, D.: J.A.M.A. 157:1274 (April 9) 1955.

'Thorazine' Hydrochloride is available in tablets, ampuls and syrup.

THORAZINE*

Smith, Kline & French Laboratories, Philadelphia 1

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.